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(54) Title: SYNTHESIS OF ACYCLIC NUCLEOSIDE DERIVATIVES

(57) Abstract

Novel intermediates and improvements in the synthesis of acyclic guanine nucleoside prodrugs of the formula (R)–9–[(2–alkanoylmethyl)–4–(aminoacyloxy)butyl]guanine (for example valtamociclovir stearate), including purine salts amenable to one pot alkylation with the acyclic side chain, acyclic 2–amino–6–halo–purine and protected guanine precursors, one pot manipulations thereof and last step work up procedures.

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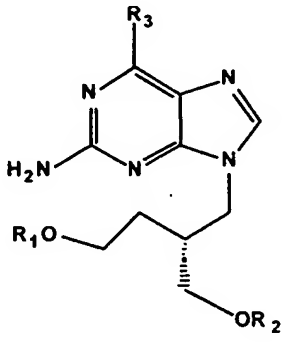
Synthesis of Acyclic Nucleoside Derivatives

Technical Field

This invention relates to the field of acyclic nucleosides and in particular to the synthesis of compounds useful against herpes and retroviral infections and novel intermediates therefore.

Background of the invention

International patent applications WO97/30051 and WO97/30052, both published 21 August 1997 the contents of which are hereby incorporated by reference, describe the preparation and antiviral activity of certain acyclic nucleosides of the formula I:



I

wherein

a) R_1 is -C(O)CH(CH(CH_3)$_2$)NH_2 or -C(O)CH(CH(CH_3)CH_2CH_3)NH_2 and R_2 is -C(O)C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl; or

b) R_1 is -C(O)C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_2 is -C(O)CH(CH(CH_3)$_2$)NH_2 or -C(O)CH(CH(CH_3)CH_2CH_3)NH_2; and R_3 is OH or H.

International patent application no WO 98/34917, the contents of which are hereby incorporated by reference and which was published on13 August

1998 (that is after the priority date of the present application) describes and claims a number of synthesis routes to the compounds above and novel intermediates therefor.

The above documents include the following preferments:

Advantageously group R_3 is hydroxy or its tautomer =O so that the base portion of the compounds of the invention is the naturally occuring guanine, for instance in the event that the side chain is cleaved in vivo. Alternatively, R_3 may be hydrogen thus defining the generally more soluble 6-deoxy derivative which can be oxidised in vivo (e.g. by xanthine oxidase) to the guanine form.

The compound of formula I may be present in racemic form, that is a mixture of the 2R and 2S isomers. Preferably, however, the compound of formula I has at least 70%, preferably at least 90% R form, for example greater than 95%. Most preferably the compound of formula I is enantiomerically pure R form.

Preferably the amino acid of group R_1/R_2 is derived from an L-amino acid.

Preferably the fatty acid of group R_1/R_2 has in total an even number of carbon atoms, in particular, decanoyl (C_{10}), lauryl (C_{12}), myristoyl (C_{14}), palmitoyl (C_{16}), stearoyl (C_{18}) or eicosanoyl (C_{20}). Other useful R_1/R_2 groups include butyryl, hexanoyl, octanoyl or behenoyl (C_{22}). Further useful R_1/R_2 groups include those derived from myristoleic, myristelaidic, palmitoleic, palmitelaidic, n6-octadecenoic, oleic, elaidic, gandoic, erucic or brassidic acids. Monounsaturated fatty acid esters typically have the double bond in the trans configuration, preferably in the -6, -9 or -11 position, dependent upon their length.

Preferably the R_1/R_2 group is derived from a fatty acid which comprises a C_9 to C_{17} saturated, or n:9 monounsaturated, alkyl.

The saturated or unsaturated fatty acid or R_1/R_2 may optionally be substituted with up to five similar or different substituents independently selected from the group consisting of such as hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, cyano, azido, oxo, mercapto and nitro, and the like.

Most preferred compounds of the formula I are those where R_1 is -$C(O)CH(CH(CH_3)_2)NH_2$ or -$C(O)CH(CH(CH_3)CH_2CH_3)NH_2$ and R_2 is -$C(O)C_9$-C_{17} saturated alkyl.

The term "lower alkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 7 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkanoyl" as used herein refers to $R_{20}C(O)$- wherein R_{20} is a loweralkyl group.

The term "alkoxy" as used herein refers to $R_{21}O$- wherein R_{21} is a loweralkyl group.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxy-carbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxy-carbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-

methylethoxycarbonyl, ,-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl gropus such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).

The term "O-protecting group" or "hydroxy-protecting group" or "-OH protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

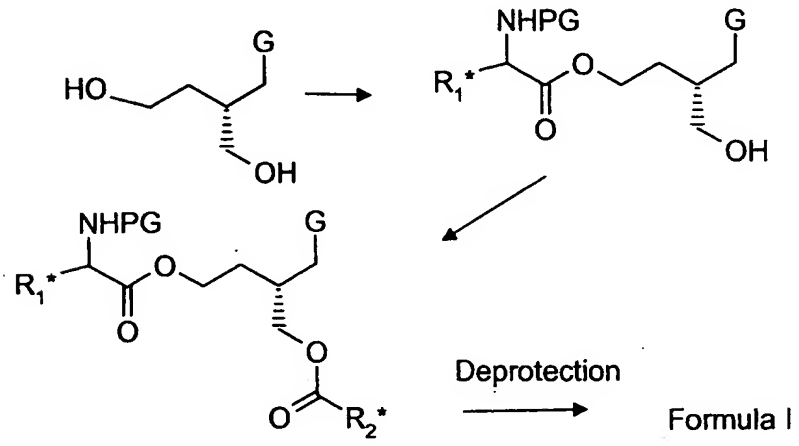
The term "activated ester derivative" as used herein refers to acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenyl derived esters, sulfonic acid derived anhydrides (for example, p-toluenesulonic acid derived anhydrides and the like) and the like.

The compounds of Formula I may be isolated as the hydrate. The compounds of the invention may be isolated in crystal form, preferably homogenous crystals, and thus an additional aspect of the invention provides the compounds of Formula I in substantially pure crystalline form, comprising >70%, preferably >90% homogeneous crystalline material, for example >95% homogeneous crystalline material.

The compounds of Formula I may be prepared from H2G as described in the documents above, namely Schemes A and B.

A. Direct acylation method

Scheme A



Scheme A depicts the preparation of compounds in which R_1 is derived from the amino acid and R_2 is derived from the fatty acid, but the converse scheme is applicable to compounds where R_1 is derived from the fatty acid and R_2 is derived from the amino acid ester. In the variant specifically depicted in scheme A above, G is guanine or 6-deoxyguanine, PG is an optional N-protecting group

or hydrogen, R_1* is the valine or isoleucine side chain and R_2* is the fatty acid chain. H2G is depicted above as a starting material but this of course may be optionally protected at R_3 or the 2 position of the purine with conventional N-protecting groups (not shown). The H2G (derivative) reacts in the first step with an activated R_1 α-amino acid derivative, as further described below, in a solvent such as dimethylformamide or pyridine, to give a monoacylated product. The R_1 α-amino acid may be suitably N-protected with N-BOC or N-CBz or the like. Under controlled conditions, the first acylation can be made to predominantly take place at the side chain 4-hydroxy group on the side chain of H2G. These controlled conditions can be achieved, for example, by manipulating the reagent concentrations or rate of addition, especially of the acylating agent, by lowering the temperature or by the choice of solvent. The reaction can be followed by TLC to monitor the controlled conditions.

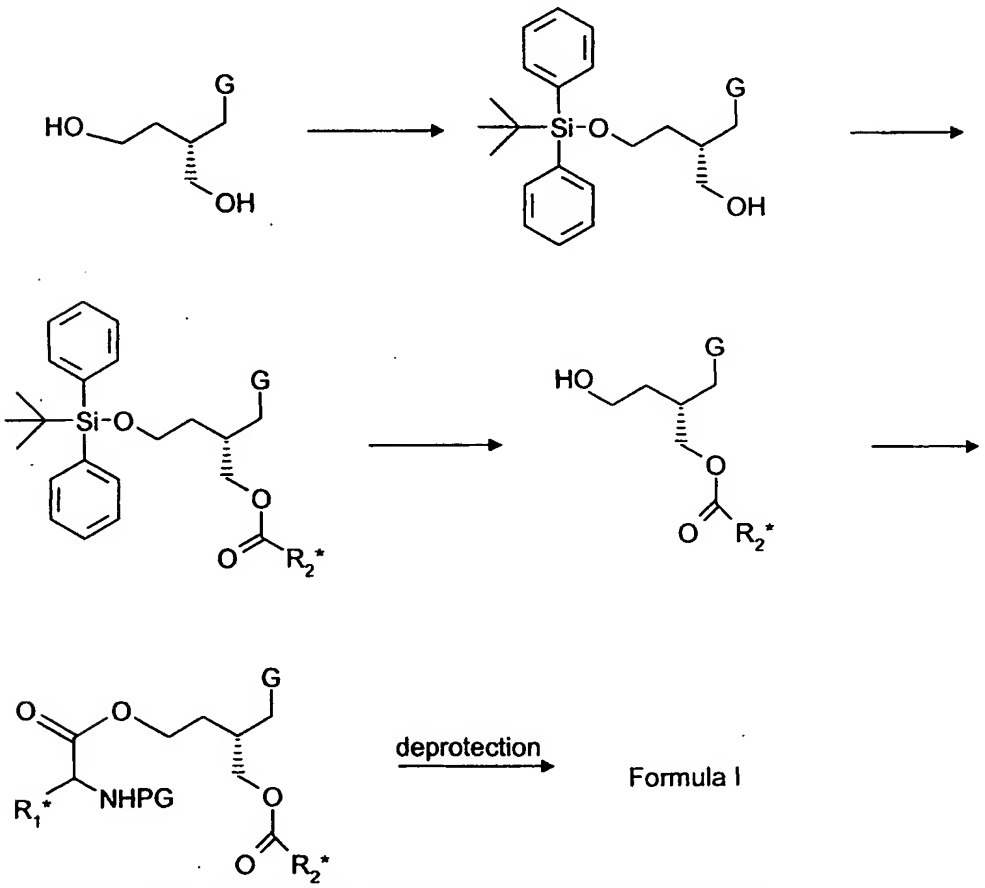
After purification, the R_1 monoacylated compounds are further acylated on the side chain 2-CH_2OH group with the appropriate activated fatty acid derivative to give diacylated products using similar procedures as for the first esterification step. The diester products are subsequently subjected to a conventional deprotection treatment using for example trifluoroacetic acid, HCl(aq)/dioxane or hydrogenation in the presence of catalyst to give the desired compound of Formula I. The compound may be in salt form depending on the deprotection conditions.

The activated R_1/R_2 acid derivative used in the various acylations may comprise e.g. the acid halide, acid anhydride, activated acid ester or the acid in the presence of coupling reagent, for example dicyclohexylcarbodiimide, where "acid" in

each case represents the corresponding R_1/R_2 amino acid or the R_1/R_2 fatty acid. Representative activated acid derivatives include the acid chloride, formic and acetic acid derived mixed anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

B. Via protection of the side chain 4-hydroxy group:

Scheme B



Formula I

wherein G, PG, R_1* and R_2* are as described for scheme A.

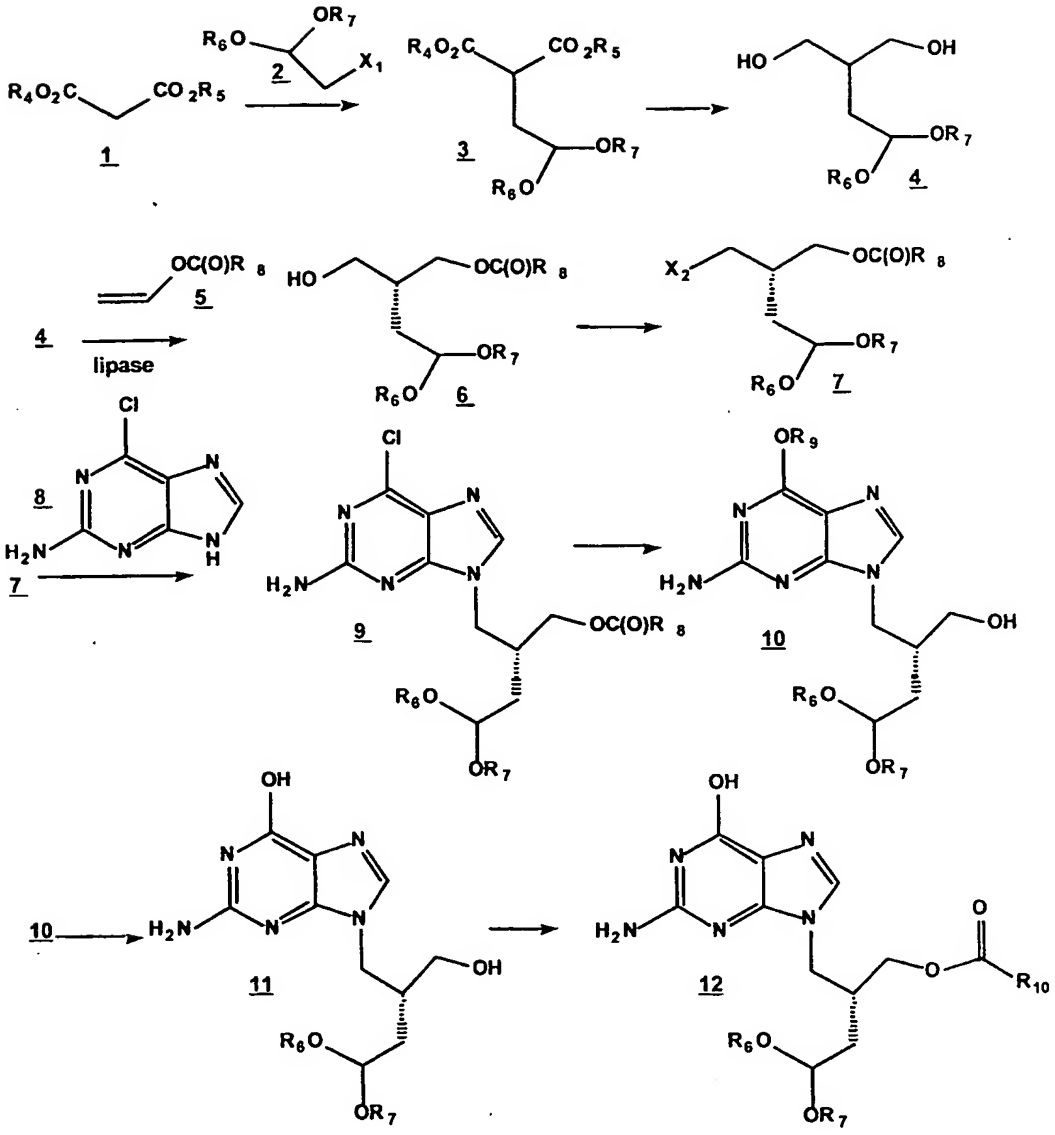
Scheme B has been exemplified with reference to the preparation of a compound where R_1 is derived from an amino acid and R_2 is derived from the fatty acid ester, but a converse scheme will be applicable to compounds where R_2 is derived from the amino acid and R_1 is derived from the fatty acid. This scheme relies on regioselective protection of the H2G side chain 4-hydroxy group with a bulky protecting group. In scheme B above this is depicted as t-butyldiphenylsilyl, but other regioselective protecting groups such as trityl, 9-(9-phenyl)xanthenyl, 1,1-bis(4-methylphenyl)-1'-pyrenylmethyl may also be appropriate. The resulting product is acylated at the side chain 2-hydroxymethyl group using analogous reagents and procedures as described in scheme A above, but wherein the activated acid derivative is the R_2 fatty acid, for example, myristic, stearic, oleic, elaidic acid chloride and the like. The thus monoacylated compounds are subjected to appropriate deprotection treatment to remove the side chain 4-hydroxy protecting group which can be done in a highly selective manner with such reagents, depending on the regioselective protecting group, as HF/pyridine and the like and manipulation of the reaction conditions, viz reagent concentration, speed of addition, temperature and solvent etc, as elaborated above. The then free side chain 4-hydroxy group is acylated with the activated α-amino acid in a similar way as described in scheme A above.

Additional techniques for introducing the amino acid ester of R_1/R_2, for instance in the schemes herein include the 2-oxa-4-aza-cycloalkane-1,3-dione method described in international patent application no. WO 94/29311.

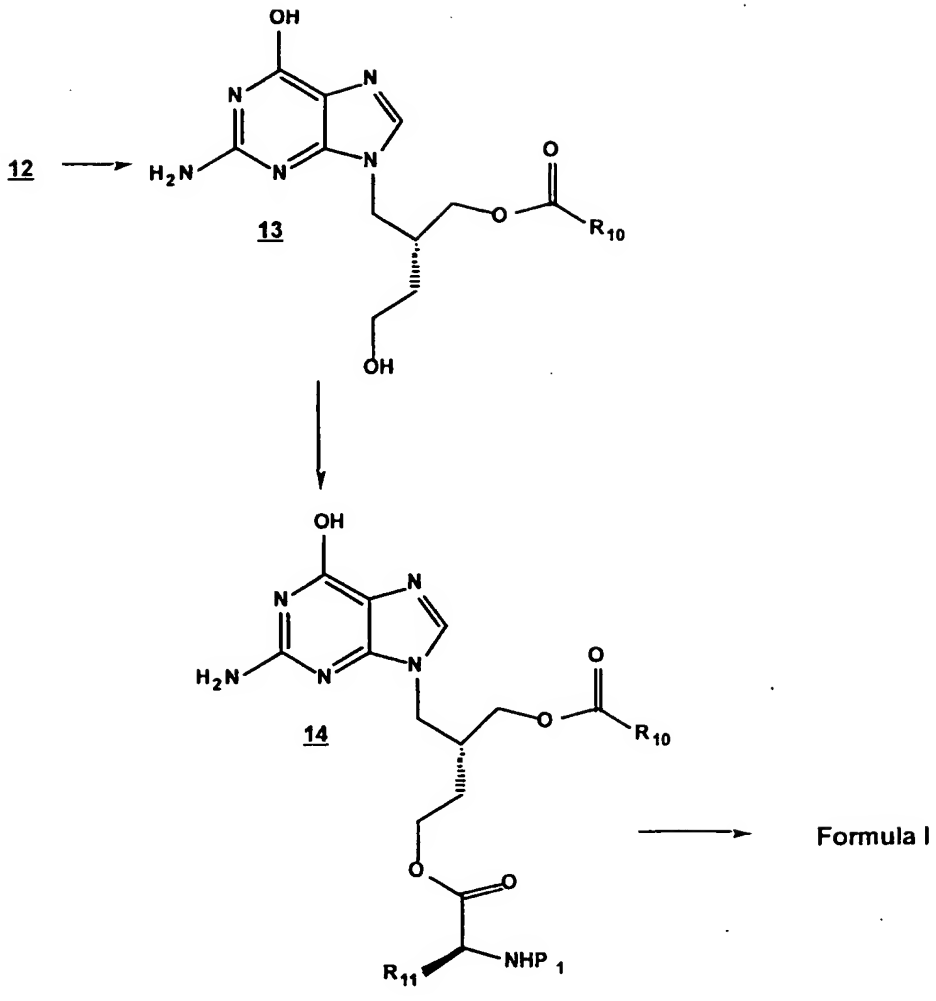
Additional techniques for introducing the fatty acid ester of R_1/R_2, for instance in the schemes herein include the enzymatic route described in Preparative Biotransformations 1.11.8 (Ed S M Roberts, J Wiley and Son, NY, 1995) with a lipase such as SP 435 immobilized Candida antarcticus (Novo Nordisk), porcine pancreatic lipase or Candida rugosa lipase. Enzymatic acylation is especially convenient where it is desired to avoid N-protection and deprotection steps on the other acyl group or the purine 2-amine.

The invention particularly relates to novel intermediates and improvements in the synthesis schemes C, D and E disclosed in the international patent applications described above.

SCHEME C


R4O2C
CO2R5
1
R6O
OR7
X1
2
3
HO
OH
4
OC(O)R8
5
lipase
6
X2
7
Cl
N
H2N
8
9
OR9
10
11
12
O
R10

SCHEME C cont'd



Referring to Scheme C, malonate 1 (R_4 and R_5 are lower alkyl or benzyl or the like) is alkylated by reaction with from about 0.5 to about 2.0 molar equivalents of acetal 2 (R_6 and R_7 are lower alkyl or benzyl and the like or R_6 and R_7 taken together are $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$and X_1 is a leaving group (for example, Cl, Br or I, or a sulfonate such as methanesulfonate,

triflate, p-toluenesulfonate, benzenesulfonate and the like)) in the presence of from about 0.5 to about 2.0 molar equivalents of a base (for example, potassium t-butoxide or sodium ethoxide or NaH or KH and the like) in an inert solvent (for example, DMF or THF or dioxane or dioxolane or N-methylpyrrolidone and the like) at a temperature of from about -40°C to about 190°C to provide alkylated malonate **3**. Alkylated malonate **3** can be purified by distillation or by first treating the crude alkylated malonate with dilute aqueous base (for example, 7% aqueous KOH), followed by removal of volatile impurities by distillation.

Reduction of **3** with from about 0.5 to about 4.0 molar equivalents of an ester to alcohol reducing agent (for example, $LiBH_4$ or $Ca(BH_4)_2$ or $NaBH_4$ or $LiAlH_4$ and the like) in an inert solvent (for example, THF or methyl t-butyl ether or t-BuOH and the like) at a temperature of from about -20°C to about 100°C provides diol **4**. Enzymatic esterification of **4** by reaction with from about 1.0 to about 20.0 molar equivalents of a vinyl ester **5** (R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl) in the presence of a lipase (for example, Lipase PS-30 or Lipase PPL or Lipase CCL and the like) or a phospholipase (for example phospholipase D and the like) provides the desired stereoisomer of ester **6**. This reaction can be carried out in the absence of solvent or in the presence of an inert solvent (for example, methyl t-butyl ether or toluene or hexane and the like). The reaction is carried out at a temperature of from about -20°C to about 80°C.

The alcohol substituent of **6** is converted to a leaving group (for example, a halogen or a sulfonate) by reaction with a halogenating agent (for example NBS/$P(Ph)_3$ or NCS/$P(Ph)_3$ or $POCl_3$ or NCS/$P(Ph)_3$/NaI in acetone and like) in an inert solvent (for example, methylene chloride or toluene or ethylacetate and the like) or by reaction with from about 0.8 molar equivalents to about 2.0 molar equivalents of a sulfonyl halide (for example, benzenesulfonylchloride, toluenesulfonylchloride or methane sulfonylchloride and the like) in the presence of from about 1.0 to about 4.0 molar equivalents of a base (for example,

triethylamine or potassium carbonate or pyridine or dimethylaminopyridine or ethyldiisopropylamine and the like) in an inert solvent (for example methylene chloride or toluene or ethylacetate or pyridine or methyl t-butyl ether and the like) at a temperature of from about -25°C to about 100°C to provide ester 7 (X_2 is a halogen or sulfonate leaving group).

Reaction of 7 with from about 0.9 to about 2.0 molar equivalents of 2-amino-6-chloropurine 8 in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium carbonate **or LiH** or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example, DMF or THF or acetonitrile or N-methylpyrrolidone or ethanol or DMSO and the like) at a temperature of from about -25 °C to about 140°C provides substituted purine 9.

Alternatively, the base can be a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

Alternatively Mitsunobu coupling (for example $P(Ph)_3$/diethyl azidocarboxylate) of alcohol 6 with 2-amino-6-chloropurine 8 provides 9.

Reaction of 9 with from about 2.0 to about 20 molar equivalents of an alcohol R_9OH (R_9 is an alcohol protecting group such as benzyl or diphenylmethyl and the like) in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium t-butoxide or potassium carbonate or NaH or KH or lithium diisopropylamide and the like) in an inert solvent (for example, THF or DMF and the like) at a temperature of from about -25°C to about 150°C provides alcohol 10.

Removal of the alcohol protecting group R_9 of **10** (for example, by catalytic hydrogenation in an inert solvent such as ethanol or benzyl alcohol or methanol or THF and the like in the presence of an hydrogenation catalyst such as Pd/C or $Pd(OH)_2$ and the like) provides substituted guanine **11**.

Esterification of **11** by reaction with a) from about 0.8 to about 2.0 molar equivalents of $R_{10}COOH$ and a coupling agent (for example DCC/DMAP) and the like in an inert solvent (for example THF or DMF and the like) or b) from about 0.8 to about 2.0 molar equivalents of an activated derivative of $R_{10}COOH$ (for example, the acid chloride or N-hydroxysuccinimide ester or $R_{10}C(O)OS(O)_2R_{30}$ (R_{30} is loweralkyl, phenyl or toluyl) or $R_{10}C(O)OC(O)R_{10}$ or $R_{10}C(O)OC(O)R_{10a}$ (R_{10a} is loweralkyl and the like) in the presence of from about 0 to about 3.0 molar equivalents of a base (for example, pyridine or dimethylaminopyridine or triethylamine or ethyldiisopropylamine or N-methylmorpholine or DBU or potassium carbonate and the like) in an inert solvent (for example, methylene chloride or THF or pyridine or acetonitrile or DMF and the like) at a temperature of from about -25°C to about 100°C provides ester **12**. R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl.

The acetal substituent of **12** is deprotected and the resulting aldehyde is reduced by first reacting **12** with from about 0.1 to about 10.0 molar equivalents of an acid (for example, triflic acid or HCl or formic acid or acetic acid/formic acid or sulfuric acid and the like) in an inert solvent (for example, THF/H_2O or methylene chloride/H_2O or ethylacetate/H_2O or ethanol/H_2O or methanol/H_2O or water and the like) at a temperature of from about -25 °C to about 100°C. To the crude reaction mixture is added from about 0.1 to about 10.0 molar equivalents of a base (for example, sodium bicarbonate or potassium carbonate or triethylamine or pyridine or KOH and the like), (optionally, additional inert solvent (for example, THF and or methylene chloride or ethylacetate or methyl t-butyl ether or isopropoanol and the like) is added) and from about 0.3 to about 5.0 molar equivalents of an aldehyde reducing agent (for example, sodium

borohydride or RaNi/H_2 or borane t-butylamine complex and the like) at a temperature of from about -25 °C to about 100°C to provide alcohol **13**. The optical purity of compound **13** can be enhanced by reaction with optically active oraganic sulfonic acids such as (S)-(+)-camphorsulfonic acid and the like. A preferred sulfonic acid for this purpose is (S)-(+)-camphorsulfonic acid.

Alternatively, the acetal substituent of **12** can be hydrolyzed by reaction in an inert solvent with an acid resin (for example, Amberlyst 15 resin, Nafion NR50 resin, Dowex 50WX4-200R resin or Amerlite 120 resin and the like) to provide the corresponding aldehyde. The aldehyde can be isolated prior to reduction to the alcohol **13** as described above or the crude aldehyde can be reduced directly *in situ*.

Reaction of **13** with from about 0.8 to about 3.0 molar equivalents of N-protected amino acid $P_1NHCH(R_{11})COOH$ or an activated derivative thereof (P_1 is an N-protecting group (for example, benzyloxycarbonyl, t-butyloxycarbonyl, allyloxycarbonyl and the like) and R_{11} is isopropyl or isobutyl) in an inert solvent (for example, THF or dioxane or dioxolane or DMF or methylene chloride and the like) at a temperature of from about 25°C to about 100°C provides alcohol **14**.

N-deprotection of **14** provides the compound of the invention of formula **I** wherein R_3 is -OH. For example, when the protecting group can be removed by hydrogenation, such as when the protecting group is Cbz, hydrogenation in the presence of Pd/C in ethanol or Pd/$BaCO_3$ or Pd/$BaSO_4$ and the like in THF or isopropanol/THF and the like is preferred.

Alternatively, compound **13** can be reacted with the symmetrical anhydride derived from $P_1NHCH(R_{11})COOH$ (i.e., $P_1NHCH(R_{11})C(O)O\text{-}C(O)CH(R_{11})NHP_1$) to provide **14**. The anhydride can be prepared *in situ* or can be separately prepared prior to reaction with **13**.

Alternatively, **11** can be prepared by hydrolysis of the ester of **9** to an alcohol (for example, by reaction with a base such as K_2CO_3, Li_2CO_3, Na_2CO_3, $KHCO_3$, LiOH, NaOH or KOH and the like in an inert solvent such as methanol,

ethanol, isopropanol, THF, water or mixtures thereof and the like, most prefereably with K_2CO_3 in MeOH/H_2O and the like), followed by direct conversion of the chloro group to an -OH (for example, by reaction with an inorganic base such as KOH or NaOH and the like in H_2O with heating and the like).

In another alternative method, **11** can be prepared directly by hydrolysis of the chloro-ester **9** (for example, by reaction with an inorganic base such as KOH or NaOH and the like in H_2O with heating and the like).

In another alternative, the ester of 9 can be hydrolyzed by an esterase in water or an aqueous buffer, with or without the presence of an added organic solvent such as an alcohol (for example, ethanol or isopropanol and the like), THF, DMF or DMSO and the like.

In another alternative method, **11** can be prepared from **9** (or from the hydroxy compound resulting from the hydrolysis of the ester in **9**) by reaction with an inorganic base (for example, NaOH, LiOH, KOH and the like, preferably, NaOH) and trimethylamine in an aqueous solvent.

In yet another alternative method, **11** can be prepared directly by hydrolysis of the chloro-ester **9** (for example, by reaction with 1-3 equivalents of a base such as sodium methoxide (and the like) in the presence of mercaptoethanol in a mixed solvent of water and methanol or dioxane (and the like) at a temperature of from about 20°C to about relfux and the like).

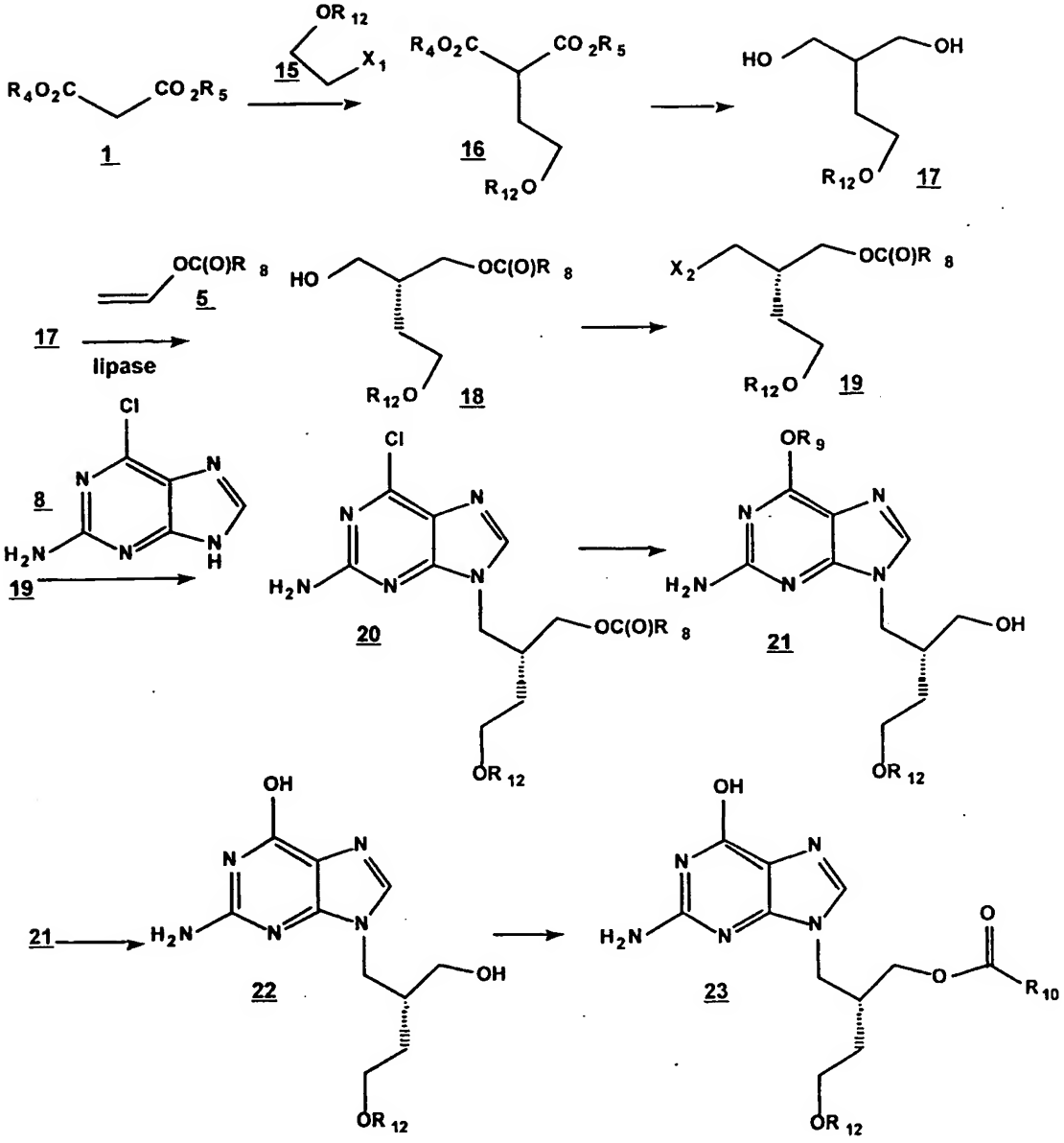
In yet another alternative method, prior to conversion of **9** to **10** or **11**, the ester of **9** can be hydrolyzed to the alcohol as described above. The alcohol can then be reesterified and purified (for example, from methyl t-butyl ether and the like). This process leads to an increase in the enantiomeric excess (i.e., purity) of the resulting ester **9**. Preferably, the alcohol is reesterified to provide the acetate, which is purified from methyl t-butyl ether.

In yet another alternative method, **13** can be prepared by reaction of **9** (wherein R_8=R_{10})with formic acid, optionally with heating, followed by reduction of the aldehyde to give **13**.

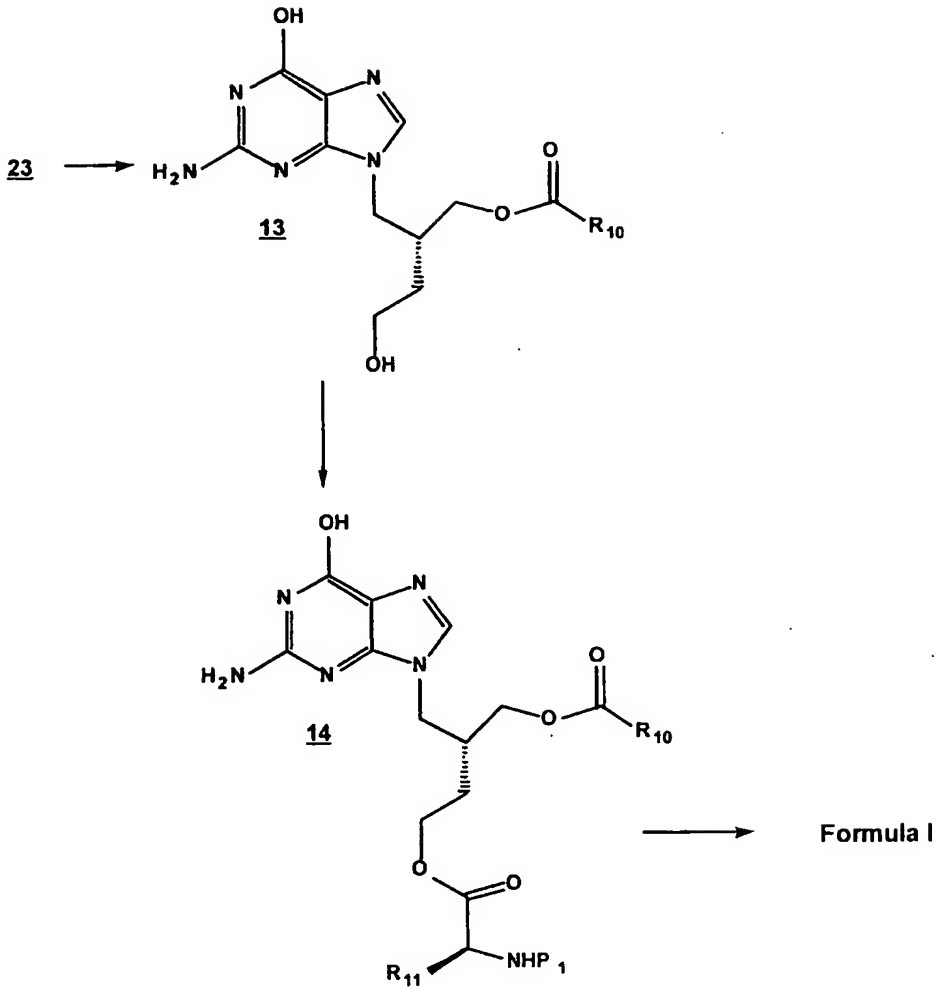
In yet another alternative, **13** can be prepared from **11** without isolation of intermediates and with *in situ* generation of the esterification agent, thus increasing purity of the resulting product and allowing increased throughput in the process.

Another alternative process for the preparation of compounds of Formula I wherein R_3 is -OH is shown in Scheme D.

SCHEME D


R4O2C
CO2R5
1
15
OR12
X1
16
R12O
HO
OH
17
OC(O)R8
5
lipase
18
X2
19
Cl
N
H2N
8
20
OR9
21
22
23
O
R10

SCHEME D cont'd



Malonate 1 (R_4 and R_5 are lower alkyl or benzyl and the like) is alkylated with from about 0.5 to about 2.0 molar equivalents of ether 15 wherein X_1 is a leaving group (for example Cl, Br or I, or a sulfonate such as methane sulfonate, triflate, p-toluenesulfonate, benzenesulfonate and the like) and R_{12} is $-CH(Ph)_2$, $-C(Ph)_3$ or $-Si(t\text{-}Bu)(Me)_2$ and the like (Ph = phenyl) in the presence of from about

0.5 to about 2.0 molar equivalents of a base (for example potassium t-butoxide or sodium ethoxide or NaH or KH and the like) in an inert solvent (for example DMF or THF or dioxane or dioxolane or N-methyl pyrrolidinone and the like) at a temperature of from about -40°C to about 190°C to provide alkylated malonate **16**.

Reduction of **16** with from about 0.5 to about 4.0 molar equivalents of an ester to alcohol reducing agent (for example $LiBH_4$ or $Ca(BH_4)_2$ or $NaBH_4$ or $LiAlH_4$ and the like) in an inert solvent (for example, THF or methyl t-butyl ether or ethanol or t-butanol and the like) at a temperature of from about -20°C to about 100°C provides diol **17**. Enzymatic esterification of **17** by reaction with from about 1.0 to about 20.0 molar equivalents of a vinyl ester **5** (R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl) in the presence of a lipase (for example, Lipase PS-30 or Lipase PPL or Lipase CCL and the like) or a phospholipase (for example phospholipase D and the like) provides the desired stereoisomer of ester **18**. The reaction can be carried out in the absence of solvent or in the presence of an inert solvent (for example methyl t-butyl ether or toluene or hexane or the like). The reaction is carried out at a temperature of from about -20°C to about 80°C.

The alcohol substituent of **18** is converted to a leaving group (for example a halogen or sulfonate) by reaction with a halogenating agent (for example $NBS/P(Ph)_3$ or $NCS/P(Ph)_3$ or $POCl_3$ or $NCS/P(Ph)_3$/NaI in acetone and the like) in an inert solvent (for example methylene chloride or toluene or ethylacetate and the like) or by reaction with from about 0.8 molar equivalents to about 2.0 molar equivalents of a sulfonyl halide (for example benzenesulfonylchloride, toluenesulfonylchloride or methane sulfonylchloride and the like) in the presence of from about 1.0 to about 4.0 molar equivalents of a base (for example triethylamine or potassium carbonate or pyridine and the like) in an inert solvent (for example, methylene chloride or toluene or ethyl acetate or methyl t-butyl

ether and the like) at a temperature of from about -25°C to about 100°C to provide ester **19** (X_2 is a halogen or sulfonate leaving group).

Reaction of **19** with from about 0.9 to about 2.0 molar equivalents of 2-amino-4-chloropurine **8** in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example potassium carbonate or LiH or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example DMF or THF or acetonitrile or N-methylpyrrolidone or ethanol and the like) at a temperature of from about -25°C to about 140°C provides substituted purine **20**.

Alternatively, Mitsunobu coupling (for example, $P(PH)_3$/diethyl azidocarboxylate) of alcohol **18** with 2-amino-4-chloropurine **8** provides **20**.

Reaction of **20** with from about 2.0 to about 20.0 molar equivalents of an alcohol R_9OH (R_9 is an alcohol protecting group such as benzyl or diphenylmethyl and the like) in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium t-butoxide or potassium carbonate or NaH or KH or lithium diisopropylamide and the like in an inert solvent (for example, THF or DMF and the like) at a temperature of from about -25°C to about 150°C provides alcohol **21**.

Removal of the alcohol protecting group R_9 of **21** (for example by catalytic hydrogenation in an inert solvent such as ethanol or benzyl alcohol or methanol or THF and the like in the presence of an hydrogenation catalyst such as Pd/C or $Pd(OH)_2$ and the like) provides substituted guanine **22**, which can be esterified as described in Scheme C (i.e., **11** to **12**) to provide **23**.

The ether substitutent of **23** is deprotected by reaction with a) a reducing agent (for example, HCO_2H and Pd/C and the like) wherein R_{12} is $-CH(Ph)_2$ or $-C(Ph)_3$, or b) a desilylating agent (for example Bu_4NF and the like) wherein R_{12} is $-Si(t\text{-}Bu)(Me)_2$ and the like to provide **13**.

Alcohol **13** can be converted to **I** as outlined in Scheme C.

Alternatively, **22** can be prepared by hydrolysis of the ester of **20** to an alcohol (for example, by reaction with K_2CO_3 in $MeOH/H_2O$ and the like), followed by direct conversion of the chloro group to an -OH (for example, by reaction with KOH in H_2O with heating and the like).

In another alternative method, **22** can be prepared directly by hydrolysis of the chloro-ester **20** (for example, by reaction with KOH in H_2O with heating and the like).

In another alternative method, **22** can be prepared from **20** (or from the hydroxy compound resulting from the hydrolysis of the ester in **20**) by reaction with an inorganic base (for example, NaOH, LiOH, KOH and the like, preferably, NaOH) and trimethylamine in an aqueous solvent.

In yet another alternative method, **22** can be prepared directly by hydrolysis of the chloro-ester **20** (for example, by reaction with 1-3 equivalents of a base such as sodium methoxide (and the like) in the presence of mercaptoethanol in a mixed solvent of water and methanol or dioxane (and the like) at a temperature of from about 20°C to about relfux and the like).

In yet another alternative method, **23** can be prepared by reaction of **20** (wherein R_8=R_{10}) with formic acid, optionally with heating, followed by reduction of the aldehyde to give **23**.

An additional alternative involves enzymatic esterification of alcohol **4** or **17** with the vinyl ester CH_2=CH-OC(O)R_{10} (i.e., R_8 = R_{10} in Schemes C and D) to directly incorporate into **6** or **18** the desired carboxylic acid ester of the final product **I**. This allows the elimination of the ester hydrolysis and reesterification involved in going from **9** to **12** or from **20** to **23**.

The processes of Schemes C and D are characterized by the fact that each of the hydroxyl groups of the acyclic side chain is differentiated by the use of different hydroxy protecting groups or precursor groups. This allows the selective acylation of each of the hydroxy groups with either an amino acid or a fatty acid group.

Yet another method for preparing compounds of Formula I is shown in Scheme E. Enzymatic esterification of **4** (see Scheme C) by reaction with from about 1.0 to about 20.0 molar equivalents of a vinyl ester **24** (R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl) in the presence of a lipase (for example, Lipase PS-30 or Lipase PPL or Lipase CCL and the like) or a phospholipase (for example phospholipase D and the like) provides the desired stereoisomer of ester **25**. This reaction can be carried out in the absence of solvent or in the presence of an inert solvent (for example, methyl t-butyl ether or toluene or hexane and the like). The reaction is carried out at a temperature of from about -20°C to about 80°C.

The alcohol substituent of **25** is converted to a leaving group (for example, a halogen or a sulfonate) by reaction with a halogenating agent (for example NBS/$P(Ph)_3$ or NCS/$P(Ph)_3$ or $POCl_3$ or NCS/$P(Ph)_3$/NaI in acetone and like) in an inert solvent (for example, methylene chloride or toluene or ethylacetate and the like) or by reaction with from about 0.8 molar equivalents to about 2.0 molar equivalents of a sulfonyl halide (for example, benzenesulfonylchloride, toluenesulfonylchloride or methane sulfonylchloride and the like) in the presence of from about 1.0 to about 4.0 molar equivalents of a base (for example, triethylamine or potassium carbonate or pyridine or dimethylaminopyridine or ethyldiisopropylamine and the like) in an inert solvent (for example methylene chloride or toluene or ethylacetate or pyridine or methyl t-butyl ether and the like) at a temperature of from about -25°C to about 100°C to provide ester **26** (X_2 is a halogen or sulfonate leaving group).

The acetal substituent of **26** is hydrolyzed to the aldehyde **27** by reacting **26** with an acid (for example, trifluoroacetic acid, triflic acid or HCl or formic acid or acetic acid/formic acid or sulfuric acid and the like) in an inert solvent (for example, THF/H_2O or methylene chloride/H_2O or ethylacetate/H_2O or ethanol/H_2O or methanol/H_2O or water and the like) at a temperature of from about -25 °C to about 100°C.

To the aldehyde **27** in an inert solvent (for example, THF and or methylene chloride or ethylacetate or methyl t-butyl ether or isopropoanol and the like) is added an aldehyde to alcohol reducing agent (for example, sodium borohydride or RaNi/H_2 or borane t-butylamine complex and the like) at a temperature of from about -25 °C to about 100°C to provide the corresponding alcohol.

Reaction of the resulting alcohol with from about 0.8 to about 3.0 molar equivalents of N-protected amino acid $P_1NHCH(R_{11})COOH$ or an activated derivative thereof (P_1 is an N-protecting group (for example, benzyloxycarbonyl, t-butyloxycarbonyl, allyloxycarbonyl, trichloroethylcarbonyl and the like) and R_{11} is isopropyl or isobutyl) in an inert solvent (for example, THF or dioxane or dioxolane or DMF or methylene chloride and the like) at a temperature of from about 25°C to about 100°C provides diester **28**.

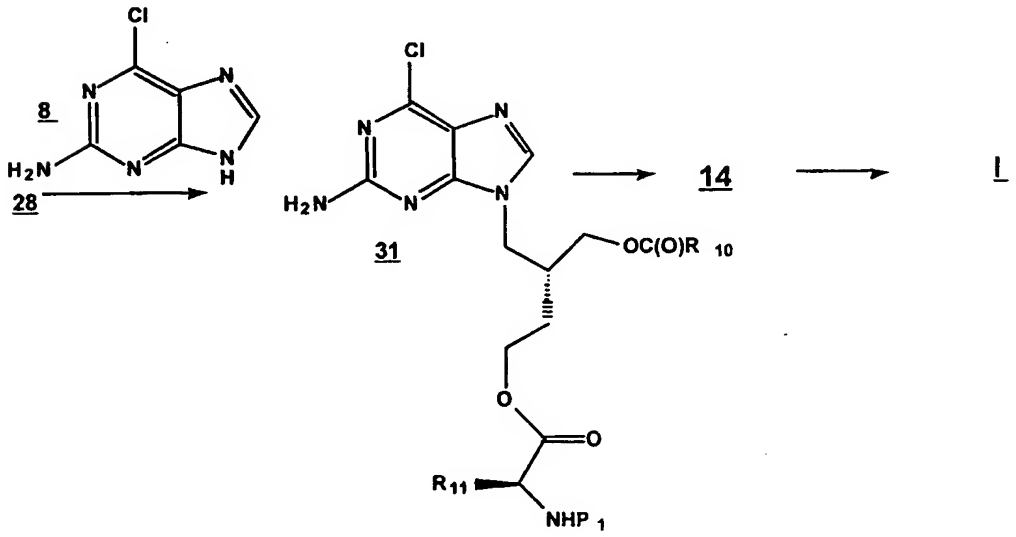
Alternatively the alcohol can be reacted with the symmetrical anhydride derived from $P_1NHCH(R_{11})COOH$ (i.e., $P_1NHCH(R_{11})C(O)O\text{-}C(O)CH(R_{11})NHP_1$) to provide **28**.

Conversion of **27** to **28** can be accomplished with or without isolation/purification of the intermediate alcohol. A preferred aldehyde to alcohol reducing agent is borane t-butylamine complex. A preferred esterification agent is the symmetrical anhydride.

Reaction of **28** with purine **29** in the presence of a base (for example potassium carbonate **or LiH** or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example, DMF and the like) provides **30**. Purine **29** is prepared from 6-chloro-2-amino purine by reaction with R_9OH in an inert solvent (for example, toluene or THF and the like) in the presence of a base (for example, NaH or KH or NaOH or KOH or potassium t-butoxide and the like). A preferred process for the the preparation of purine **29** involves reaction of 2-amino-6-chloropurine with neat R_9-OH in the presence of a base such as NaOH or KOH or potassium t-butoxide and the like. Substituted purine **30** is deprotected to provide the compound of Formula **I**.

Alternatively, in the reaction of **28** with **29**, the base can be a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

SCHEME F

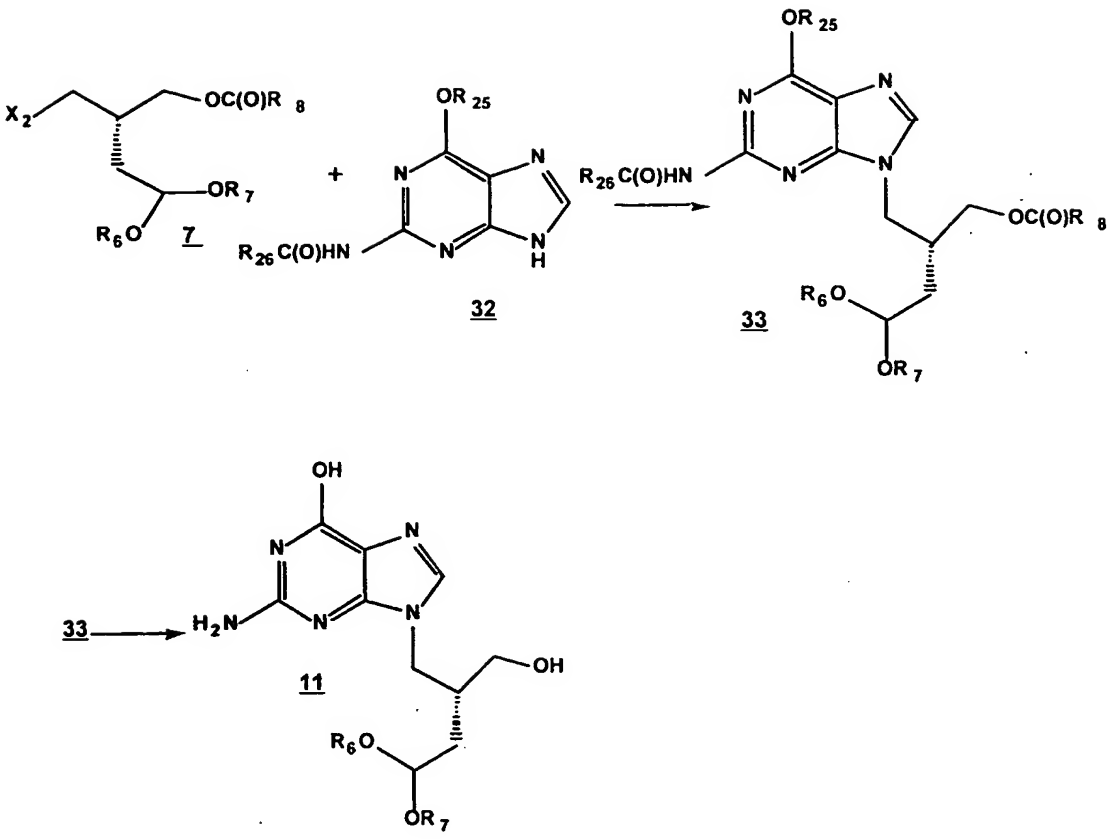


Yet another method for preparing compounds of Formula I is shown in Scheme F. Reaction of **28** with amino-chloropurine 8 in the presence of a base (for example potassium carbonate or LiH or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example, DMF THF and the like) provides **31**. Hydrolysis of **31** to **14** can be accomplished under basic or acidic conditions (for example, with trimethlyamine or DABCO or KOH or LiOH or NaOH and the like in water/THF or methylene chloride and the like or with acetic acid and the like).

Alternatively, **8** can be be alkylated with **28** using a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

In each of Schemes C, D and F, the 2-amino-6-chloro-purine (**8**) can be replaced with 2-amino-6-iodo-purine or 2-amino-6-bromopurine, which can be alkylated and then transformed to the substituted guanine in a manner analogous to that disclosed for alkylation and transformation of **8**.

SCHEME G



Yet another method for preparing the compounds of formula I is shown in Scheme G. Alkylation of **32** with **7** in the presence of a base (for example, potassium carbonate, LiH, NaH and the like) in an inert solvent (for example, DMF THF and the like) provides **33**. R_{25} is hydrogen or $-C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group. R_{26} is loweralkyl, phenyl or benzyl.

Hydrolysis of **33** to **11** can be accomplished under basic conditions (for example, with KOH in water and the like).

Alternatively, 32 can be alkylated with 7 using a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

Detailed Description of the Invention

Example 1

Alternative preparation of (R)-9-[4,4-diethoxy-2-(hydroxymethyl)-butyl]guanine

A 50 gallon stainless steel reactor was purged with nitrogen and charged with the product of Example 30 a) of WO 98/34917 (13.5 kg) and DMAP (0.48 kg). To the solids was added methyl t-butyl ether (108 kg), followed by triethylamine (4.0 kg). Acetic anhydride (4.64 kg) was added last. The resulting mixture was stirred at ambient temperature for 30 minutes. Distilled water (56 kg) was charged to the reactor and the contents were stirred for 30 minutes. After allowing the mixture to settle for 30 minutes, the lower layer was drained and 50 kg of saturated brine was added to the reactor. The contents of the reactor were stirred for 30 minutes and let settle for 30 minutes. The lower layer was drained and a Karl Fischer reading was done on the organic layer to assure that the water content was less than 2.5%. The organic layer was stirred at ambient temperature for 24 hours. The resulting precipitate was filtered off and the filtrate was concentrated under vacuum, followed by a methanol (22 kg) chase. To the resulting residue was added methanol (49 kg) and 10.8 kg of a 50% aqueous KOH solution. The mixture was heated to relux for one hour. The

methanol was removed by distillation and the distillation residue was diluted with distilled water (112 kg) and 9.2 kg of a 50% aqueous KOH solution. The resulting mixture was heated to reflux for 16 hours. The contents of the reactor were cooled to 25°C and were then adjusted to pH 7.0 using 37% aqueous acetic acid solution. The internal temperature of the reactor was then adjusted to 10°C and the contents stirred for 30 minutes. The resulting slurry was centrifuged and the resulting wet cake was charged back to the reactor. To the cake was charged distilled water (70 kg). The internal temperature was adjusted to 50°C and the contents were stirred for 30 minutes. Then the internal temperature was adjusted to 20°C and the contents stirred for 30 minutes. The resulting slurry was centrifuged and the cake rinsed once with distilled water (15 kg). The cake was transferred to dryer trays and dried at 45°C under vacuum for 18 hours to provide the desired product as a pale yellow powder (8.6 kg, 99% ee).

Example 2

Alternative preparation of (R)-9-[4-hydroxy-2-(stearoyloxymethyl)butyl]-guanine

To a 2 liter round bottom, 3-neck flask equipped with a nitrogen inlet, temperature probe, rubber septum and mechanical stirrer was charged stearic acid (25.0 g), THF (525 mL) and triethylamine (12.2 mL). The resulting solution was cooled to -30°C using an ice/salt bath. Pivaloyl chloride (10.3 mL) was added slowly via a syringe, maintaining the reaction temperature at less than 5°C. The resulting slurry was stirred at 0 ±5°C for 2 hours. The ice bath was removed and the reaction allowed to warm to room temperature. The resulting precipitate was filtered and the filter cake was rinsed with THF (100 mL). The resulting clear filtrate was added to a 3 liter 3-neck flask (equipped with a nitrogen inlet and mechanical stirrer) charged with the product of Example 1 (22.5 g) and DMAP (1.7 g). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 18°C and a room temperature solution of 1:1

aqueous triflic acid (27.5 g triflic acid) was added slowly, maintaining the temperature at less than 23°C. The resulting solution was stirred at approximately 22C for 4.5 hours. Then the reaction mixture was cooled to 18°C and diulted with water (70 mL). Sodium bicarbonate was added to adjust the pH to 6-7 (target 6.5). The mixture was stirred at room temperature for 30 minutes.

The bath temperature was set at 35°C and the borane-t-butylamine complex (4.52 g) was added in several portions over 50 minutes. The reaction mixture was stirred at 35°C overnight. An additional portion of borane-t-butylamine (200 mg) was added and the mixture stirred for an additional 3 hours. The reaction mixture was quenched by pouring it into a cold solution of 5 mL of HCL in 625 mL of water. The resulting pH was 5-6 (target less than pH 6). The resulting mixture was stirred for 3 hours at room temperature and then filtered. The filter cake was dried overnight under house vacuum at 35°C. The filter cake,optionally, can be washed with acetonitrile prior to drying. The dried solid was suspended in acetone (1100 mL) and heated to reflux. The slurry was held at reflux for 30 minutes and then cooled to room temperature. After stirring at room temperature for one hour, the mixture was filtered. The filter cake was air-dried on the filter funnel for 30 minutes and then suspended in THF (350mL). The THF mixture was heated to reflux and water (35 mL) was added. The flask containing the mixture was removed from the heating bath and allowed to cool. When the temperature reached less than 30°C, ethyl acetate (1050ml) was added and the mixture was stirred for one hour at room temperature. The resulting slurry was filtered and the filter cake was dried overnight at 35°C to provide the desired product as a white powder (30.4 g).

Example 3

Alternative preparation of (2S)-4-N-Carbonylbenzyloxy-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate

The product of Example 31 c) of WO 98/34917 (6.00 g) was dissolved in THF (60 mL). Borane t-butylamine comlex (0.48 g) was added neat at room temperature. The reaction mixture was stirred at room temperature for 1.25 hours. The pH was adjusted to 7-8 by addition of 5% aqueous HCl. The reaction mixture was diluted with THF (60 mL) and was washed with 20% brine (40 mL) and then again with saturated brine (30 mL). The organic solution was filtered through a pad of silica gel, dried over magnesium sulfate (6.0 g) for one hour and filtered. The filtrate was added to the product of Example 37 a) of WO98/34917 (7.0 g) and DMAP (70 mg). The mixture was stirred under nitrogen at room temperature for about 3 hours. An additional amount of the product of Example 37 a) (0.5 g) was added and the mixture was stirred overnight at room temperature. An additional amount of the product of Example 37 a) (0.5 g) was added and the mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate (90 mL) and washed with half-saturated sodium bicarbonate (90 mL), with brine (60 mL), with 5% KH_2PO_4 (60 mL) and brine (60 mL). The organic solution was dried over sodium sulfate and concentrated to provide the desired product as a yellow oil (6.88 g).

Example 4

(R)-2-Amino-6-chloro-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

A 100 ml round bott0m 3-neck flask was charged with lithium hydride (58 mg, 7.3 mmol) and DMF (10 mL). 2-Amino-6-chloropurine (1.14 g, 6.72 mmol) was added al at once at room temperature. The mixture was stirred at room temperature for 40 minutes under nitrogen. The product of Example 31 d) of WO98/34917 (5.2 g, 6.72 mmol) as a solution in DMF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred at 40-50°C under nitrogen for 27 hours. The reaction mixture was cooled to room

temperature and poured into a separatory funnel containing ethyl acetate (100 mL) and 5% aqueous KH_2PO_4 (100 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was concentrated under vacuum. The crude product was dissolved in methylene chloride (5 mL) and chromatographed on flash silica gel (10 g) (eluent: 1% methanol/methylene chloride (1000 mL), 5% methanol/methylene chloride(250 mL)) to provide the desired product (3.06 g).

Example 5

Alternative preparation of (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]guanine

A 25 mL round bottom flask was charged with the product of Example 4 (0.2 g, 0.26 mol), triethylamine (0.20 mL of 40% aq. solution), THF (4 mL) and water (1 mL). The resulting solution was stirred at room temperature for 20 hours. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL). This solution was dried over sodium sulfate and the solvent was evaporated under vacuum. The crude product was chromatographed on flash silica gel (10 g) (eluant: 1/10 methanol/methylene chloride (400 mL)) to give the desired product as a colorless oil (0.15 g).

Example 6

Alternative preparation of (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]guanine

The product of Example 4 (145 mg, 0.188 mol) was dissolved in glacial acetic acid (1.9 mL) and the solution was heated to 110°C for 3 hours. The solution was then cooled to room temperature and the acetic acid was removed by distillation under reduced pressure. The residue was dissolved in ethyl

acetate and washed with water, aqueous sodium bicarbonate and bringe. The organic solution was evaporated under reduced pressure to give the desired product (134 mg).

Example 7

Alternative preparation of (R)-2-Amino-6-chloro-9-[4,4-diethoxy-2-(hydroxymethyl)butyl]purine

DBU (36.8 g, 0.24 mol) was added to a suspension of 2-amino-6-chloropurine (41 g, 0.24 mol) in DMF (340 mL) at room temperature under nitrogen. After 5 minutes, the product of Example 14 d) of WO98/43917 (85 g, 0.22 mol) was added. The mixture was stirred at 40-45°C for 15-20 hours. Then the mixture was diluted with methyl t-butyl ether (340 mL), toluene (340 mL), water (340 mL) and brine (340 mL). After mixing for 15 minutes, the organic layer was separated and the aqueous layer was extracted with toluene (2 x 300 mL). The combined organic layer was washed with water (500 mL) and concentrated under vacuum at 60°C bath temperature. The resulting oil was diluted with methanol (260 mL) and cooled to 5°C. A solution of K_2CO_3 (16 g, 0.12 mol) in water (65 mL) was added over 15 minutes maintaining the reaction mixture temperature below 10°C. The mixture was stirred at 10°C for 1 hour. Then the mixture was diluted with brine (500 mL) and stirred for 30 minutes. The resulting solid was filtered, washed with 5% methanol in water (50 mL) and the filter cake was dried to give the desired product as a white solid (39 g).

Example 8

Alternative preparation of (R)-2-Amino-6-chloro-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]purine

2-Amino-6-chloropurine (0.6 g, 3.6 mmol) and tert-butylimino-tri(pyrrolidino)phosphorane (1.1 g, 3.6 mmol) were mixed in anhydrous THF (4 mL) for 10 minutes at 40°C. The product of Example 14 d) of WO98/34917(1.16 g, 3.0 mmol) was added and the mixture was stirred at 41-43°C overnight. The THF was removed by evaporation under vacuum and the residue was diluted with methyl t-butyl ether (10 mL), water (5 mL) and brine (5 mL). The organic layer was separated and the aqueous layer was extracted with toluene (2 x 10 mL). The combined organic layer was washed withwater (25 mL) and concentrated under vacuum. The residue was slurried with methyl t-butyl ether (12 mL) and water (0.1 mL) and filtered. The filtrate was concentrated under vacuum and slurried with hexane (10 mL) and methyl t-butyl ether (1 mL). The resulting solid was filtered and dried to provide the desired product (0.73 g).

Example 9

Alternate preparation of (R)-2-Amino-6-chloro-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

The title compound was prepared following the procedure of Example 8, but substituting the product of Example 31 d) of WO98/34917 for the product of Example 14 d) of WO98/34917.

Example 10

Alternate preparation of (R)-2-Amino-6-chloro-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

The title compound can be prepared following the procedure of Example 9, but substituting DBU for tert-butylimino-tri(pyrrolidino)-phosphorane.

Example 11

2-Amino-6-iodopurine

To a 2 liter single-neck round bottom flask with a mechanical stirrer was charged 2-amino-6-chloropurine (41.0 g, 242 mmol). The flask was cooled in an ice-water bath. The the reaction flask was charged HI (47% solution, pre-cooled in a refrigerator, 250 mL) in one portion. The resulting suspension was stirred for 16 hours at ice-water bath temperature. Water (500 mL) was charged to the reaction flask. The suspension was stirred at 0°C for 1 hour. The precipitate was filtered and washed with water (3 x 250 mL). The filter cake was transferred to a 250 mL filtration flask. 6 M NaOH solution (85 mL) was added to the solid through the filter to rinse out residual solid and wash into the filter flask. The solution obtained was added slowly to a boiling solution of acetic acid (25 mL) and water (250 mL). The resulting suspension was cooled to room temperature and stirred at room temperature for 2 hours. The solid was collected by centrifugation, washed with water (2 x 250 mL), followed by heptane (250 mL). The solid was first spin-dried on the centrifuge for 30 minutes and then dried in a vacuum oven overnight to provide the desired product (61.3 g).

Example 12

Alternative preparation of (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]guanine

a) (R)-2-Amino-6-iodo-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

To a 50 mL single neck round bottom flask was charged the product of Example 31 d) of WO98/34917 (2.0 g, 2.58 mmol), 2-amino-6-iodopurine (0.742 g, 2.84 mmol), DBU (o.425 mL) and DMF (10 mL). The reaction mixture was

stirred for 20 hours at 40°C. Ethyl acetate (30 mL) was added to the reaction mixture and stirring continued for 30 minutes. The reaction mixture was filtered and the filtered solid was washed with ethyl acetate (2 x 30 mL). The filtrate and washings were combined and washed with water (3 x 25 mL). The organic solution was evaporated under vacuum. The residue was redissolved in ethyl acetate (50 mL) and again evaporated under vacuum to azeotropically remove any residual water, providing the desired product (2.1 g).

^{1}H NMR (300 MHz, d_6-DMSO) : 8.06 (s, 1H), 7.36 (br s, 5H), 6.78 (br s, 2H) 3.85-4.2 (m, 9H), 2.15 (t, 2H), 0.8-1.7 (m, 43H)
Mass Spec. (ESI): 863 $(M+H)^+$

b) Alternative preparation of (R)-2-Amino-6-iodo-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

The desired product was obtained following the procedure of Example 12 a) with the replacement of DBU by K_2CO_3 (1.5 g).

c) (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]-guanine

The product of Example 12 a) (3.4 g, 3.94 mmol), acetonitrile (45 mL), water (35 mL), acetic acid (45 mL) and sodium acetate (3.05 g) were mixed and heated to reflux (86-87°C) for 30 hours. The volatile solvent was removee by evaporation under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined extracts were mixed with saturated sodium bicarbonate (2 x 100 mL) for 30 minutes. The organic layers were separated and washed with saturated sodium bicarbonate (100 mL), followed by water washes (3 x 100 mL). The organic solvent was evaporated under reduced pressure. To the residue was added anhydrous ethyl acetate (3 x 200 mL), with

evaporation of the solvent each time under reduced pressure, to provide a solid. The solid was recrystallized from refluxing acetonitrile (50 mL). After cooling the acetonitrile mixture to room temperature, it was allowed to stand at room temperature overnight and then was cooled to -13°C for 30 minutes. The resulting solid was collected by filtration, washed with acetonitrile (2 x 10 mL) and dired in a vacuum oven to provide the desired product (2.4 g).

Example 13

(R)-2-Amino-6-iodo-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]purine

To a 100 mL single neck round bottom flask was charged the product of Example 14 d) of WO 98/34917 (9.3 g, 23.9 mmol), 2-amino-6-iodopurine (4.8 g, 18.4 mmol), DBU (3.6 mL, 24.0 mmol) and DMF (50 mL). The mixture was stirred for 16 hours at 45°C. The reaction mixture was cooled to room temperature and ethyl acetate (250 mL) was added and stirring continued for 30 minutes. The reaction mixture was filtered and the filtered solid was washed with ethyl acetate (2 x 125 mL). The filtrate and washings were combined and washed with water (4 x 50 mL). The organic solution was evaporated under reduced pressure. Ethyl acetate (50 mL) was added to the residue and evaporated under reduced pressure. Methyl t-butyl ether (300 mL) was added to the residue and stirred. The resulting solid was filtered and dried to provide the desired product (8.8 g).

(K_2CO_3 can be used in place of DBU in the above procedure to provide the desired product).

^{1}H NMR (300 MHz, $CDCl_3$): 7.81 (s, 1H), 5.12 (br s, 2H), 4.61 (t, 1H), 4.16 (m, 1H), 4.04 (m, 2H), 3.62 (m, 2H), 3.48 (m, 2H), 2.52 (m, 1H), 2.03 (s, 3H), 1.79 (s, 1H), 1.69 (m, 2H), 1.19 (m, 6H).

Example 14

Alternative preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine

a) Preparation of (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]-guanine.

To a 500 mL round bottom flask was added the product of Example 30 e) of WO98/34917 (10.4 g, 20.0 mmol), the product of Example 37 a) (11.7 g, 24.2 mmol), DMAP (52 mg, 0.43 mmol) and THF (170 mL). The mixture was stirred at room temperature for 4 hours. Water (10 mL) was added and the solvent was evaporated under reduced pressure (bath temperature of approximately 45°C). Residual THF was chased with ethyl acetate (40 mL). The residue was dissolved in ethyl acetate (200 mL) and the solution was washed with saturated sodium bicarbonate (3 x 100 mL) and then water (100 mL) and the organic solution was evaporated under reduced pressure (bath temperature of approximately 45°C). Residual ethyl acetate was chased with isopropanol (25 mL) to provide the desired product in crude form as 14 g of an orange, sticky solid.

b) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine.

To the flask containing the crude product of Example 14 a) was added isopropanol/THF (4/1, 100 mL) and the mixture was heated to 45-50°C to dissolve the solids. The solution was cooled to room temperature. To a separate 500 mL round bottom flask was added 10% Pd/C (1.00 g) and the flask was evacuated and back-filled with nitrogen three times. Then isopropanol/THF (4/1, 25 mL) was added. The solution of the product of Example 14 a) was then added to the catalyst flask, along with two 35 mL isopropanol/THF (4/1) rinses. The reaction flask was then evacuated and back-filled with hydrogen three times. The solution was then heated to 40-45°C for 16 hours. Then the hydrogen-filled

balloon was replaced with a condenser and the reaction mixture was heated to 65°C for 25 minutes. The reaction mixture was then filtered through celite (6.05 g) and the filter cake was washed with isopropanol/THF (4/1, 2 x 50 mL). The filtrate was concentrated under vacuum (bath temperature 45°C) and residual THF was chased with isopropanol (50mL).

To the flask was added isopropanol (50 mL) and the mixture was heated to about 80°C to dissolve the solids. Isopropyl acetate (150 mL) was added and heating was continued to dissolve the solid which formed. Once all solids were dissolved, the solution was cooled to room temperature and stirred for 12 hours. The resulting solid was filtered and dried to provide a light gray solid (9.0 g). This solid was added to a 500 mL round bottom flask, along with activated carbon (2.25 g) and isopropanol (200 mL). The mixture was heated to 60-65°C for 1 hour and then filtered through celite (6.00 g). The celite cake was washed with hot isopropanol (65°C, 2 x 50 mL) and the filtrate was concentrated under reduced pressure (bath temperature of 50°C). Isopropanol (40 mL) was added to the residue and the mixture was heated to 80°C to dissolve the solids. Isopropyl acetate (120 mL) was added and heating was continued to dissolve the precipitate which formed. The solution was cooled to room temperature and stirred for 12 hours. The resulting solid was filtered and dried to give the desired product as a white solid (7.7 g).

Alternatively, the crude product of the hydrogenation reaction was mixed with isopropanol (50 mL) and the mixture was heated to 65-70°C to dissolve the solids. Acetonitrile (65 mL) was added dropwise via an addition funnel at a rate to maintain the temperature above 55°C. During addition of the acetonitrile, a fluffy gray precipitate formed. After addition of the acetonitrile was complete, the mixture was heated at 65°C for 30 minutes and then filtered through a pad of celite in a steam jacketed funnel. The filtrate was concentrated and residual acetonitrile was chased with isopropanol (70 mL). The resulting solid was recrystallized from isopropanol/isopropyl acetate (30/90 mL) and after stirring at

room temperature for 6 hours, the solid was filtered and dried to give the desired product as a white solid (6.72 g).

Example 15

Alternative preparation of (R)-9-[4,4-diethoxy-2-(hydroxymethyl)butyl]-guanine

a) 2-N-Acetyl-6-O-diphenylcarbamoyl-(R)-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]-guanine.

To a 50 mL round bottom flask was added 2-N-acetyl-6-O-diphenylcarbamoylguanine (1.10 g, 2.83 mmol) and anhydrous DMF (10 mL). DBU (423 µL, 2.83 mmol) was added and the solid dissolved after stirring for 5 minutes. A solution of the product of Example 14 d) of WO98/34917 (1.0 g, 2.6 mmol) in anhydrous DMF (5.0 mL) was added and the resulting solution was stirred at 45°C under nitrogen for 28 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (40 mL) and water (20 mL). The organic layer was separated and washed with a 5% $KHSO_4$ solution, a saturated sodium bicarbonate solution and brine and then dried over sodium sulfate. The solvent was evaporated under vacuum to provide a light yellow oil, which was chromatographed on silica gel (5% heptane in ethyl acetate) to provide the desired product as a light yellow solid (460 mg).

^{1}H NMR (300 MHz, $CDCl_3$) _ 1.05-1.18 (m, 6H), 1.55-1.68 (m, 2H), 1.92 (s, 3H), 2.40-2.52 (m, 1H), 2.47 (s, 3H), 3.32-3.46 (m, 2H), 3.48-3.62 (m, 2H), 3.89-4.02 (m, 2H), 4.10-4.25 (m, 2H), 4.52 (t, J=5.4 Hz, 1H), 7.05-7.42 (m, 10H), 7.91 (s, 1H), 8.11 (s, 1H)
ESI (-) MS m/z 603 $(M-H)^-$.

b) (R)-9-[4,4-diethoxy-2-(hydroxymethyl)butyl]-guanine

To the product of Example 15 a) (100 mg, 0.165 mmol) in a 25 mL round bottom flask was added KOH (62 mg, 0.972 mmol) and water (10 mL). The suspension was refluxed for 20 hours. The reaction mixture was cooled to room temperature and acidified to pH 5 using acetic acid. The solvent was evaporated under reduced pressure to provide the desired product as a white solid.

Example 16

2-N-Acetyl-(R)-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]-guanine

To a 50 mL round bottom flask was added 2-N-acetyl-guanine (547 mg g, 2.83 mmol) and the product of Example 14 d) of WO98/34917(1.0 g, 2.6 mmol). Anhydrous DMSO (10 mL) was added, folowed by DBU (430 µL, 2.88 mmol). The resulting solution was stirred at 40°C under nitrogen for 24 hours. After cooling to room temperature, the reaction mixture was diluted with chloroform (50 mL) and water (20 mL). The organic layer was separated and washed with water (2x) and brine and then dried over sodium sulfate. The solvent was evaporated under vacuum to provide a light yellow oil, which was chromatographed on silica gel (10% methanol in ethyl acetate) to provide the desired product as a white foam (280 mg).

N-7 isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.31 (m, 6H), 1.62-1.85 (m, 2H), 2.06 (s, 3H), 2.44 (s, 3H), 2.50-2.68 (m, 1H), 3.40-3.56 (m, 2H), 3.57-3.73 (m, 2H), 3.96-4.20 (m, 2H), 4.32-4.55 (m, 2H), 4.62 (t, J=5.5 Hz, 1H), 7.82 (s, 1H), 11.60 (s, 1H), 12.40 (s, 1H).

N-9 isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.28 (m, 6H), 1.66-1.72 (m, 2H), 2.02 (s, 3H), 2.36 (s, 3H), 2.38-2.52 (m, 1H), 3.38-3.53 (m, 2H), 3.54-3.70 (m, 2H), 3.93-4.15

(m, 4H), 4.58 (t, J=5.3 Hz, 1H), 4.58 (t, J=5.3 Hz, 1H), 7.75 (s, 1H), 10.67 (s, 1H), 12.23 (s, 1H).

Example 17

Alternative preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine

To a 500 ml 3-neck round bottom flask equipped with a magnetic stirrer and a temperature probe was added the product of Example 30f) of WO98/34917 (5.5 g), THF (65 mL) and isopropanol (65 mL). The clear solution was purged three times with nitrogen and 5% $Pd/BaCO_3$ (0.6 g) was added. The mixture was stirred at 40°C under a hydrogen filled balloon for 16 hours. The reaction mixture was filtered through celite and the filtrate was evaporated to dryness to provide a white solid. The solid was dissolved in isopropanol (25 mL) at 70°C and isopropyl acetate (100 mL) was added. The resulting mixture was cooled to room temperature and stirred for 1 hour. The resulting solid was filtered and dried under vacuum to provide the desired product as a white solid (3.39 g).

Example 18

Alternative preparation of 2-Amino-6-benzyloxypurine

To a 500 mL 3 neck round bottom flask equipped with a magnetic stirrer, temperature probe and nitrogen inlet was added 2-amino-6-chloropurine (20 g), sodium hydroxide (28 g) and benzyl alcohol (200 mL). The mixture was stirred for 20 minutes and then heated at 100°C for 2-3 hours. The reaction mixture was then cooled to room temperature and partitioned between methyl t-butyl ether (300 mL) and water (300 mL). The aqueous layer was separated and the pH was adjusted to 7-8 with 6 M HCl. The resulting solid was filtered, washed with

water (50 mL) and dried under vacuum at 50°C for 20 hours to provide the desired product as a pale yellow solid (24.3 g).

Example 19

Alternative preparation of (3S)-3-stearoyloxymethyl-4-toluenesulfonyloxy-butyraldehyde

To a 1 liter 3 neck round bottom flask equipped with a magnetic stirrer, temperature probe and nitrogen inlet was added the product of Example 31 b) of WO98/34917(40 g) and THF (320 mL). The solution was cooled to 20°C and a solution of trifluoromethane sulfonic acid (20 g) and water (20g) was added. After stirring for 2-3 hours, the reaction mixture was quenched with sodium bicarbonate (12.0 g), followed by addition of methyl t-butyl ether (500 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (200 mL), water (200 mL) and brine (200 mL) and then was dried over sodium sulfate. The organic solution was evaporated to dryness under vacuum to give a pale yellow oil which was dissolved in hexane (300 mL) and stirred overnight. The resulting solid was filtered and dried under vacuum to give the desired product as a white solid (25.6 g).

Example 20

Alternative preparation of (3S)-3-stearoyloxymethyl-4-toluenesulfonyloxy-butyraldehyde

To a 100 mL 3 neck round bottom flask equipped with a magnetic stirrer, temperature probe and a nitrogen inlet was added the product of Example 31 b) of WO98/34917 (6.5 g), acetic acid (30 mL) and formic acid (20 mL). After stirring at room temperature for 20 minutes, water (20 mL) was added to the mixture and stirring was continued at room temperature for 30 minutes. The

resulting precipitate was filtered and dried for 1.5 hours. The solid was added to a 100 mL flask, followed by addition of hexane (90 mL). The mixture was stirred overnight. The resulting solid was filtered and dried at 40°C udner vacuum for 20 hours to provide the desired product as a white solid (4.6 g).

Example 21

Alternative preparation of N-Carbobenzyloxy-L-valine Anhydride

A solution of N-Benzyloxycarbonyl-L-valine (20.0 g) in isopropyl acetate/toluene (1:1. 80 mL) was cooled to 0°C. A solution of DCC (8.2 g) in toluene (20 mL) was added slowly, at a rate such that the internal temperature of the reaction mixture was kept below 10°C. The addition funnel was washed with toluene (20 mL). The reaction mixture was stirred for 1 hour and then allowed to warm to room temperature and stirred for another 1 hour. The reaction mixture was filtered and the filter cake was washed with toluene (20 mL). Heptane (120 mL) was added to the filtrate and the resulting solution was cooled to 0-5°C and stirred for 1 hour. The resulting solid was filtered and washed with heptane (20 mL) and then dried under vacuum at 35°C for 18 hours to provide the desired product as a white solid (17.0 g).

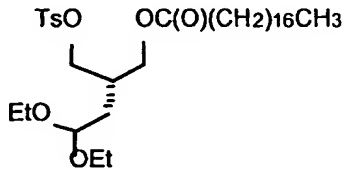
Example 22

Alternative preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine

a) Preparation of (2R)-4,4-Diethoxy-2-stearoyloxymethyl-butanol. Vinyl stearate (3202 g, 9.375 moles) was charged to a 12 liter 4 neck Morton flask with nitrogen inlet and mechanical stirring. Heating was applied via a 50°C water bath. As the vinyl stearate melted, the water bath temperature was decreased to 35°C and stirring was started.

Heating and stirring was continued until the vinyl stearate was completely melted. Then the product of Example 14 b) of WO98/34917 (1800 g, 9.375 moles) and Lipase PS30 (45 g, 2.5 wt%) were added. The suspension was stirred at 35-37°C for 22 hours. The reaction mixture was quenched by addition of 37.5% methyl t-butyl ether in heptane (2.5 L). The mixture was then filtered through celite and the celite was washed with 37.5% methyl t-butyl ether in heptane (12 L). The organic filtrates were combined and washed with water (10 L) and 23% NaCl solution (10 L). The organic solution was evaporated and methylene chloride was aded (4 L). The solution was evaporated to about half of its original volume. An additional 4 L of methylene chloride was added and the solution was allowed to stand at 5°C overnight.

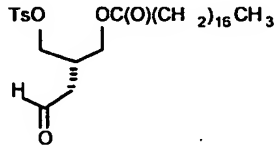
b) Preparation of (2S)-4,4-Diethoxy-2-stearoyloxymethyl-butyl toluenesulfonate.



The methylene chloride product solution resulting from Example 22 a) was added to a 50 L round bottom flask equipped with mechanical stirring, water condenser, nitrogen inlet and a temperature probe. An additional 4 L of methylene chloride was added, followed by triethylamine (2349 g, 23.2 moles) and p-toluenesulfonyl chloride (2654 g, 13.92 mol). The reaction mixture was stirred for 6 hours without external heating or cooling. Water (1.8 L) was added to the reaction mixture and stirred vigorously for 17 hours. The organic layer was separated and washed with water (10 L). The aqueous layer was extracted with

methylene chloride (1 L). The combined organic layers were washed with 7% sodium bicarbonate solution (10 L) and 23% NaCl solution (10 L). The solvent was evaporated to provide the desired product as a thick oil (5947 g).

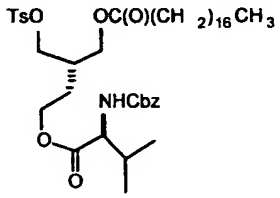
c) Preparation of (3S)-3-stearoyloxymethyl-4-toluenesulfonyloxy-butyraldehyde.



A suspension of the product of Example 22 c) (4573 g, 7.47 mol) in acetonitrile (4 L) was added to a 50 L reactor equipped with a thermocouple and nitrogen inlet. An additional 13 L of acetonitrile was added and the suspension was heated to 37°C with steam. A solution of triflic acid (1253 mL, 14.16 mol) in water (7.6 L) was added over 20 minutes. Then the mixture was stirred at 39-42°C for 1 hour. The reaction mixture was quenched by adding it to 20 L of 23% aqueous sodium bicarbonate solution and 35 L of methyl t-butyl ether. The reaction flask was rinsed with 5 L of methyl t-butyl ether and an additional 20 L of 23% aqueous sodium bicarbonate was added. This mixture was stirred for 10 minutes and the layers were separated. The organic layer was washed with a mixture of 25 L of 23% aqueous sodium bicarbonate solution and 15 L of 7% NaCl solution. Then the organic layer was washed with 25 L of 7% NaCl solution. The solvents were removed on a batch concentrator to provide a thick slurry. Heptane (32 L) was added to the slurry and then evaporated. Additional heptane (12 L) was added and evaporated. A further amount of heptane (40 L) was added and the suspensin was heated to 44°C in 60 minutes, causing complete dissolution. The reaction flask was cooled to 40°C in 10 minutes by running cold water over the surface of the flask. The solution was then allowed

to slowly cool to 35°C, where cyrstallization occurs. The resulting thick mixture was stirred for 14 hours. The precipitate was filtered and rinsed twice with 4 L of heptane and then dried on the filter funnel for 2 hours and then in a vacuum oven with nitrogen purge for 60 hours at room temperature. The resulting solid (3200 g), heptane (30 L) and methyl t-butyl ether (1.6 L) were combined and heated with stirring to dissolution. The resulting solution was cooled over 1 hour to 42°C and the resulting suspension was stirred for 20 hours while cooling to room temperature. The precipitate was filtered and dried in a vacuum oven with nitrogen purge for 20 hours at room temperature to give the desired product (2860 g).

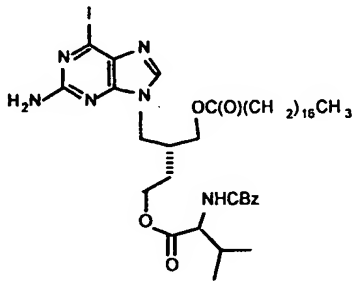
d) Preparation of (2S)-4-N-Carbonylbenzyloxy-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate.



A solution of the product of Example 22 c) (511 g, 950 mmol) in THF (2.55 L) was stirred at ambient temperature in a high-pressure reactor with Raney Ni (383 g wet weight) under a 40 psi atmosphere of hydrogen for 2 hours. The suspension was filtered and the filtrate was swirled with magnesium sulfate (250 g) for 1 hour. The organic solution was filtered and added to N-Cbz-L-valine anhydride (598 g, 1.23 mol) and DMAP (5.8 g, 47.5 mmol) and stirred at ambient temperature for 20 hours. The reaction mixture was poured into 5% KH_2PO_4 (2.5 L) and extracted with methyl t-butyl ether (2.5 L). The organic layer was washed with 10% potassium carbonate (2 x 2.5 L) and then 23% NaCl solution (2.5 L). The volatiles were evaporated and methyl t-butyl ether (1 L) was added. The

volatiles were again evaporated and this procedure repeated (usually about three times) until the Karl-Fischer test indicated less than 1 mole% water. The organic solution was then concentrated and stored as an approximately 65% w/w solution of the desired product.

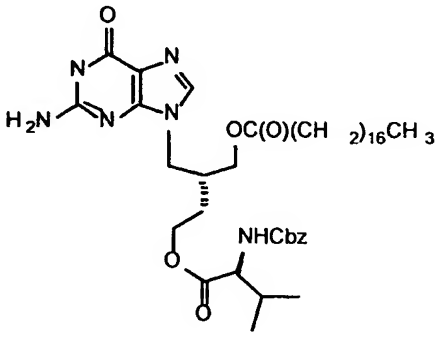
e) Preparation of 2-Amino-6-iodo-(R)-9-[(2-stearoyloxymethyl)-4-(N-benzyloxycarbonyl-L-valyloxy)butyl]purine.



To a 500 mL flask equipped with a stir bar and a nitrogen inlet was added (2S)-4-N-Carbonylbenzyloxy-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate (21.8 g, 28.2 mmol), 2-amino-6-iodopurine (9.73 g, 37.3 mmol) and potassium carbonate (11.88 g, 86.1 mmol) slurried in DMF (155 mL). The resulting mixture was stirred for 16 hours at 50°C. The mixture was then cooled to room temperature and poured into 400 mL of ethyl acetate and washed with water (3 x 400 mL). The aqueous washes were combined and extracted with isopropyl acetate (50 mL). The organic extracts were combined, washed with brine (200 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was dissolved in acetonitrile (150 mL) and washed with heptane. The bottome layer was separated and concentrated. The residue was dissolved in methylene chloride (200 mL). Silica gel (60 g) was added and stirred for 10 minutes. This mixture was poured into a funnel containing 40 g of silica gel. The product was eluted off of the silica gel by washing with 4/1 methyl t-butyl

ether/heptane.The filtrate was concentrated to provide the desired product (19.6 g).

f) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(N-benzyloxycarbonyl-L-valyloxy)butyl]guanine.



Into a 300 mL Fisher-Porter bottle (stirbar/nitrogen) was placed the product of Example 23 e) (12.36 g, 14.34 mmol) dissolved in acetonitrile (98 mL) and glacial acetic acid (98 mL), followed by addition of sodium acetate trihydrate (11.70 g, 86 mmol). The resulting mixture was stirred at 120°C for 4 hours. The mixture was cooled to room temperature and poured into 400 mL of methyl t-butyl ether. The mixture was washed with 5% aq. NaCl (2 x 300 mL), 2 M potassium carbonate (150 mL), 1% $NaHSO_3$ (100 mL) and brine (100 mL). The organic layer was concentrated under vacuum. The residue was dissolved in heptane (150 mL) and extracted with acetonitrile (2 x 100 mL). The top layer (heptane) was concentrated to give the desired product as a thick syrup (8.98 g).

g) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(valyloxy)butyl]-guanine.

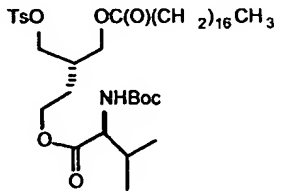
Into a 100 mL shaker was placed (R)-9-[(2-stearoyloxymethyl)-4-(N-benzyloxycarbonyl-L-valyloxy)butyl]guanine (4.53 g, 6.03 mmols) dissolved in

isopropanol (45 mL), followed by addition of 4% Pd/C (450 mg). The resulting mixture was shaken under a 5 psi hydrogen for 3 days. The mixture was filtered and concentrated under vacuum to provide a waxy solid. This material was dissolved in hot isopropanol (12 mL) and isopropyl acetate was added (24 mL). The mixture was slowly cooled to 40°C and then stirred at 0°C for 1 hour. The precipitate was filtered and washed with isopropyl acetate (5 mL) and then dried to provide the desired product (1.53 g).

Example 23

Alternative preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine

a) Preparation of (2S)-4-N-t-butyloxycarbonyl-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate.

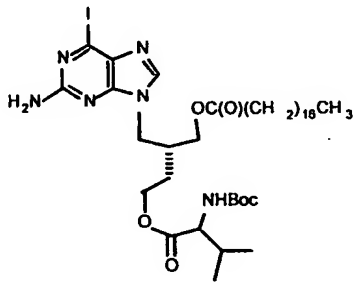


A solution of the product of Example 22 c) (3.10 g, 5.75 mmol) in THF (50 mL) was stirred at ambient temperature in a high-pressure reactor with Raney Ni (5 g wet weight) under a 5 psi atmosphere of hydrogen for 3 hours. The suspension was filtered and the filtrate was swirled with magnesium sulfate (8 g). The organic solution was filtered and N-Boc-L-valine anhydride (3.11 g, 7.47 mmol) was added, followed by DMAP (0.105 g). The resulting mixture was stirred at ambient temperature for 30 minutes. The mixture was cooled to 0°C and treated with N,N-dimthylethylenediamine (125 mg). The resulting solution was stirred for 20 minutes and poured into methyl t-butyl ether (100 mL) and was

washed with 5% KH_2PO_4 (100 mL), 1 M potassium carbonate (100 mL) and then 27% NaCl solution (20 mL). The organic solution was then concentrated under vacuum to provide the desired product (3.67 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 0.95 (d, 3H), 1.25 (m, 30 H), 1.45 (s, 9H), 1.55 (m, 2H), 1.70 (m, 2H), 2.1 (m, 1H), 2.21 (t, 2H), 2.46 (s, 3H), 3.94-4.2 (m, 6H), 5.0 (m, 1H), 7.37 (m, 2H), 7.78 (m, 2H). Mass Spec.=740 $(M+H)^+$

b) Preparation of 2-Amino-6-iodo-(R)-9-[(2-stearoyloxymethyl)-4-(N-t-butyloxycarbonyl-L-valyloxy)butyl]purine.



To a 100 mL flask equipped with a stir bar and a nitrogen inlet was added the product of Example 23 a) (3.67 g, 4.97 mmol), 2-amino-6-iodopurine (1.68 g, 6.46 mmol) and potassium carbonate (2.05 g, 14.9 mmol) slurried in DMF (27 mL). The resulting mixture was stirred for 16 hours at 50°C. The mixture was then cooled to room temperature and poured into 100 mL of ethyl acetate and washed with KH_2PO_4 (100 mL containing 20 mL of brine). The organic phase was washed with brine (2 x 75 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in acetonitrile (20 mL) at 50°C. The mixture was cooled to room temperature and stirred for 2 hours. The precipitate was filtered, washed with acetonitrile (2 x 5 mL) and dried to provide the desired product (2.79 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (m, 6H), 0.95 (d, 3H), 1.25 (m, 30 H), 1.43 (s, 9H), 1.6 (m, 2H), 1.74 (m, 2H), 2.1 (m, 1H), 2.28 (t, 2H), 2.52 (m, 1H), 4.1-4.4 (m, 6H), 5.03 (m, 1H), 5.22 (s, 1H), 7.73 (s, 1H). Mass Spec.=829 $(M+H)^+$

c) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(N-t-butyloxycarbonyl-L-valyloxy)butyl]-guanine.

Into a 4 mL vial (stir bar/nitrogen) was placed the product of Example 23 b) (0.076 g, 0.092 mmol) dissolved in acetonitrile (0.444mL) and glacial acetic acid (0.444 mL), followed by addition of sodium acetate trihydrate (0.031 g). The resulting mixture was stirred at 100°C for 16 hours. HPLC analysis of the mixture indicated that the desired product had been obtained, by comparison with authentic product obtained as described in Example 17 b) of WO98/34917.

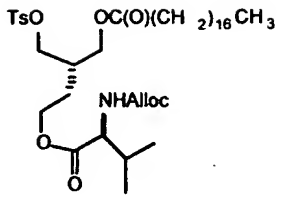
d) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(valyloxy)butyl]-guanine.

Into a 20 mL vial (stirbar/nitrogen) was added (R)-9-[(2-stearoyloxymethyl)-4-(N-t-butyloxycarbonyl-L-valyloxy)butyl]-guanine (0.218 g, 0.29 mmol) dissolved in methylene chloride (3.1 mL) and trifluoroacetic acid (0.33 mL). The resulting mixture was stirred at 25°C for 14 hours. The mixture was diluted with methylene chloride (10 mL), washed with 7% sodium bicarbonate, dried over magnesium sulfate and concentrated under vacuum to provide the desired product (161 mg).

Example 24

Alternative preparation of (R)-9-[(2-stearoyloxymethyl)-4-(L-valyloxy)butyl]-guanine

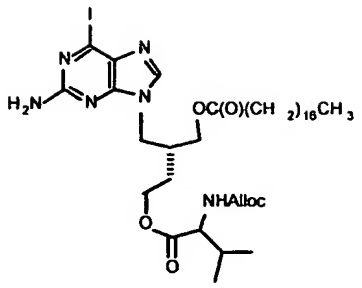
a) Preparation of (2S)-4-N-allyloxycarbonyl-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate.



A solution of the product of Example 22 c) (15.0 g, 27.7 mmol) in THF (100 mL) was stirred at ambient temperature in a high-pressure reactor with Raney Ni (16 g wet weight) under a 5 psi atmosphere of hydrogen for 3 hours. The suspension was filtered and the filtrate was swirled with magnesium sulfate (8 g). The organic solution was filtered and N-Alloc-L-valine anhydride (13.82 g, 43.3 mmol) was added, followed by DMAP (0.203 g). The resulting mixture was stirred at ambient temperature overnight. The mixture was diluted with methyl t-butyl ether (120 mL) and was washed with 5% KH_2PO_4 (25 mL), 1 M potassium carbonate (100 mL) and then 27% NaCl solution (20 mL). The organic solution was then concentrated under vacuum to provide the desired product (20.6 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 0.95 (d, 3H), 1.25 (m, 30 H), 1.55 (m, 2H), 1.70 (m, 2H), 2.12 (m, 1H), 2.20 (t, 2H), 2.46 (s, 3H), 3.94-4.25 (m, 6H), 4.57 (m, 2H), 5.20-5.35 (m, 3H), 5.90 (m, 1H), 7.45 (m, 2H), 7.79 (m, 2H).

b) Preparation of 2-Amino-6-iodo-(R)-9-[(2-stearoyloxymethyl)-4-(N-allyloxycarbonyl-L-valyloxy)butyl]purine.



To a 500 mL flask equipped with a stir bar and a nitrogen inlet was added the product of Example 24 a) (18.43 g, 25.4 mmol), 2-amino-6-iodopurine (8.61 g, 33.0 mmol) and potassium carbonate (10.51 g, 76.2 mmol) slurried in DMF (137 mL). The resulting mixture was stirred for 16 hours at 50°C. The mixture was then cooled to room temperature and poured into 394 mL of isopropyl acetate and washed with water (3 x 400 mL). The organic phase was washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in acetonitrile (200 mL). The mixture was stirred for 3 hours at room temperature. The precipitate was filtered, washed with acetonitrile (2 x 25 mL) and dried to provide the desired product (12.28 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (m, 6H), 0.98 (d, 3H), 1.29 (m, 30 H), 1.6 (m, 2H), 1.74 (m, 2H), 2.13 (m, 1H), 2.28 (t, 2H), 2.52 (m, 1H), 3.9-4.4 (m, 6H), 4.58 (d, 2H), 5.20-5.35 (m, 3H), 5.90 (m, 1H), 7.76 (s, 1H). Ic Mass Spec.=813 $(M+H)^+$

c) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(N-allyloxycarbonyl-L-valyloxy)butyl]-guanine.

Into a 60 mL sealed tube (stir bar) was placed the product of Example 24 b) (1.00 g, 1.23 mmol) dissolved in acetonitrile (6.0 mL) and glacial acetic acid (6.0 mL), followed by addition of sodium acetate trihydrate (1.00 g). The resulting mixture was stirred at 120°C for 4 hours. The mixture was cooled to room temperature and poured into 15 mL of methyl t-butyl ether, washed with5% NaCl

(2 x 15 mL), 2 M potassium carbonate (2 x 20 mL), 1% $NaHSO_3$ (2 x 15 mL) and brine (15 mL). The organic phase was concentrated under vacuum. The residue was chromatographed on silica gel (9/1 methylene chloride/methanol) to provide the desired product as a wax (0.67 g).

^1H NMR (300 MHz, d_6-DMSO): δ 0.85 (m, 9H), 1.21 (m, 30 H), 1.45 (m, 2H), 1.62 (m, 2H), 1.99 (m, 1H), 2.22 (t, 2H), 2.35 (m, 1H), 3.8-4.0 (m, 4H), 4.12 (t, 2H), 4.46 (m, 2H), 5.15-5.3 (m, 2H), 5.88 (m, 1H), 6.38 (b s, 2H), 7.63 (s, 1H), 10.52 (b s, 1H). Ic Mass Spec.=703 $(M+H)^+$

d) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(valyloxy)butyl]-guanine.

Into a 4 mL vial (stirbar/nitrogen) was added the product of Example 24 c) (0.07 g, 0.10 mmol) dissolved in THF (1.0 mL) and triphenylphosphine (1.6 mg) and $Pd_2(dba)_3$ (1.4 mg) and pyrrolidine (0.071 g). The resulting mixture was stirred at 25°C for 14 hours. The mixture was concentrated under vacuum, diluted with isopropanol and stirred at 4°C. The resulting precipitate was filtered to provide the desired product (33 mg).

Example 25

Diazobicycloundecenium Salts of 2-Amino-6-substituted-purines

Using a strong and neutral organic base capable of substantially compete deprotonation of a purine base allows *in situ* preparation of reasonably soluble purine salts. These are beneficial for synthetic purposes, being efficiently alkylated under relatively mild conditions. Advantageously, the salts of the invention are formed without the

concomitant production of water experienced when employing, for instance conventional glycosylation/alkylation bases such as tetrabutylammonium hydroxide. This water production with conventional bases necessitates the isolation and desiccation of the salt prior to reaction with the alkylating agent and are thus not suited to one pot reaction schemes. Additionally, many primary, secondary and tertiary amines (eg triethylamine and diazobicycloocatane) have inadequate basicity to irreversibly deprotonate purines and thus do not deprotonate 6-chloropurines but rather substitute the 6-halogen instead. Diisopropylethylamine (Hünigs base) has been proposed in the alkylation of N-acetylguanines, but is ineffective in the preparation of, say (R)-9-[4,4-diethoxy-2-acetoxymethyl)butyl]guanine, when alkylating 2-amino-6-chloropurine with 2S-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate. In contrast, when DBU is used as a base to produce the salts exemplified above, a surprisingly clean reaction is observed. This reaction is quite unexpected as DBU was believed to be less basic than Hünigs base (Schwesinger, R Chimia 1985, 39, 269-272 footnote 13). In addition DBU is known to be an excellent eliminating reagent (in particular in aprotic solvents) and at elevated temperatures so decomposition of the alkylating reagent was primarily expected under these conditions. It appears likely that DBU is capable of deprotonating (halo)purines and indeed the sparely soluble 2-amino-6-chloropurine goes into solution in a couple of minutes when treated with one equivalent of DBU in DMF. Such a solution can precipitate the captioned salt in 90% yield, as can the corresponding THF solution.

For synthetic purposes, isolation of the diazobicycloundecenium salt, such as the title compounds may not be required. Thus these purine derivatives prepared in situ can be alkylated in solvents such as DMSO

or DMF at 40-45° with similar efficiency, but greater cleanliness as conventional tetrabutylammonium salts or purine in conjunction with K_2CO_3.

The respective 2-amino-6-substituted-purine (3 mmol), I,8-diazabicyclo[5.4.0]undecene (0.46 g, 3 mmol), and DMF (2.5 mL) or THF (5 mL) were mixed at room temperature for 0.5 h. The precipitate was filtered off, washed with (t-butyl methyl ether (10 mL), and dried under vacuum to give the salts indicated below:

Diazobicycloundecenium salt of 2-amino-6-chloropurine

90 % yield.

'H NMR (DMSO-d_6 δ): 1.5 - 1.7 (m, 6 H), 1.89 (m. 2 H), 2.68 (m, 2 H), 3.27 (m, 2 H), 3.43 (m, 2 H), 3.50 (m, 2 H), 5.69 (s, 2 H), 7.70 (s, 1 H).

^{13}C NMR (DMSO- d_6 δ): 19.1 (CH_2), 23.5 (CH_2), 26.1 (CH_2), 28.3 (CH_2), 31.7 (CH_2), 37.8 (CH_2), 47.8 (CH_2), 53.2 (CH_2), 126.2 (C), 145.1 (C), 153.4 (CH), 157.4 (C), 164.5 (C), 165.0 (C).

Diazobicycloundecenium salt of 2-amino-6-benzyloxypurine

80 % yield.

'NMR (DMSO-d_6 δ): 1.6 (m, 6H), 1.8 (m, 2 H), 2.5 (m, 2 H), 3.18 (m, 2 H), 3.25 - 3.4, (m, 4 H), 5.48 (s, 2 H), 5.93 (s. 2 H), 7.25 - 7.45 (m, 3 H), 7.5 (m, 2 H), 7.71 (s. 1 H).

^{13}C NMR (DMSO-d_6 δ): 19.8 (CH_2), 24.1 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 32.5 (CH_2), 38.9 (CH_2), 47.7 (CH_2), 52.8 (CH_2), 66.4 (CH_2), 113.8 (C). 127.8 (CH), 128.3 (4C, CH), 137.2 (C), 143.5 (CH), 158.5 (C), 159.0 (C), 160.1 (C), 163.9 (C).

Diazobicycloundecenium salt of 2-amino-6-iodopurine

92 % yield.

^{1}NMR (DMSO- d_6 δ): 1.5-1.7 (m, 6 H), 1.9 (m, 2 H), 2.62 (m, 2 H), 3.27 (t, 6 Hz, 2 H), 3.44 (t, 6 Hz, 2 H), 3.52 (m, 2 H), 5.67 (s, 2 H), 7.66 (s, 1 H).

^{13}C NMR (DMSO- d_6 δ): 19.1 (CH_2), 23.5 (CH_2), 26.1 (CH_2), 28.3 (CH_2), 31.6 (CH_2), 37.8 (CH_2), 47.8 (CH_2), 53.2 (CH_2), 118.6 (C), 133.5 (C), 151.6 (CH), 157.6 (C), 159.6 (C), 165.1 (C).

Typical Procedure for Alkylation of Various Purine Derivatives.

Purine (3.6 mmol), a base (3.6 mmol) and a solvent [THF (4.5 mL), DMF (3 mL),or DMSO (2.5 mL)] were stirred at 40 - 41°C for 15 h under nitrogen atmosphere. The reaction mixture was transferred into a 25 mL volumetric flask and diluted with THF to the volume. An aliquot of this solution (2 ± 0.02 mL) was transferred into another 25 ml flask and diluted with water (0.5 mL) and THF to the volume. Resulting solution was analyzed by HPLC for the peak area of the desired product. The yield was obtained by adjusting to the corresponding peak area of a known amount of the isolated pure material. Each reaction was repeated at least twice. Each HPLC analysis - three times. The accuracy of analyses was within 3 % range. The ratios of isomeric alkylation products were determined from 'H NMR spectra (300 or 400 MHz, DMSO- d_6) of crude reaction mixtures (after solvent removal or from reactions ran in DMSO-d_6 directly) by integration of sharp singlets from protons at C^8.

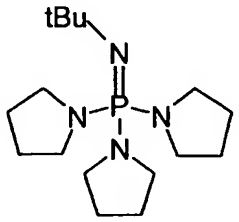
purine	Alkylating agent	solvent	Yield Σ N9 +N7	Ratio N9:N7
2-amino-6-chloropurine	A	DMF	79	4.1
2-amino-6-chloropurine	A	DMSO	85	4.0
2-amino-6-chloropurine	B	DMF	75	3.0
2-amino-6-chloropurine	B	DMSO	66	3.4
2-amino-6-BnO-purine	A	DMF	85	1.6
2-amino-6-BnO-purine	A	DMSO	81	1.7

A: (2S)-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate

B: cyclopentyltosylate

Example 26

tert- Butyliminotri(pyrrolidino)phosphorane 2-amino-6-substituted purine salts



tert- Butyliminotri(pyrrolidino)phosphorane salts of various purines were prepared in situ by adding 1.1 g, 3.6 mmol of the bulky phosphorane depicted above to a slurry of 2-amino-6-substituted purine in THF (4 mL). The mixture was heated to 40 °C and stirred for 10 min without isolation of the salt.

The alkylation efficiency of the purine salts thus prepared without isolation from a bulky phosphazine base was compared with conventional alkylating approaches unsing the process described in Example 25. In particular the relevant tosylate, ie (2S)-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate or cyclopentyltosylate (3.3 mmol) was added via syringe. The mixture was stirred at 40 - 43 °C overnight. The solvent was evaporated and the residue was diluted with methyl *tert*-butyl ether (10 mL), water (5 mL) and brine (5 mL). Organic layer was separated and aqueous layer was extracted with toluene (2 x 10 mL). The combined organic layer was washed with water (25 mL) and concentrated under vacuum. The residue was slurried in methyl *tert*-butyl ether (12 mL) and water (0.1 mL) then filtered. The filter cake was washed with methyl *tert*-butyl ether (mL) and dried to provide the 7-isomer isomer (R)-2-amino-6-chloro-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (0.1 g, 10 %). The filtrate was concentrated in vacuo and slurried with hexane (10 mL) and methyl *tert*-butyl ether (1 mL). The resulting solid was filtered and dried to provide the N-9 isomer (R)-2-amino-6-chloro-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (0.73 g, 71%). The regioisomers of the 2-amino-6-chloro-7/9-cycloclopentylpurines and the (R)-2-amino-6-benzyloxy-7/9-(2-acetoxymethyl-4,4-diethoxybutylpurines were extracted analogously and separated by column chromatography.

Data analysis was as described in Example 25

(R)-2-amino-6-chloro-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine
Yield 71%

'HNMR (DMSO-d_6 δ): 1.1 (m, 6 H), 1.55 (m, 2 H), 1.98 (s, 3 H), 2.45 (m, 1 H), 3.3 - 3.6 (m, 6 H), 3.95 (d, 2 H), 4.1 (d, 2 H), 4.5 (t, 1 H), 6.9 (s, 2 H), 8.15 (s, 1 H).

^{13}C NMR (DMSO-d_6 δ): 15.1 (2 C, CH_3), 20.5 (CH), 32.7 (CH_2), 33.9 (CH_3), 44.8 (CH_2), 60.6 (CH_2), 61.0 (CH_2), 64.2 (CH_2), 100.4 (CH), 123.2 (C), 143.5 (CH), 149.3 (C), 154.4 (C), 159.7 (C), 170.2 (C).

Anal. Calcd. for C16H24ClN504: C, 49.81; H, 6.27; N, 18.15. Found: C, 50.24, H, 6.41, N, 17.94.

(R)-2-amino-6-chloro-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine

'HNMR (DMSO-d_6 δ): 1.01(t, 7Hz, 3H), 1.04 (t, 7 Hz, 3 H) 1.42 - 1.67 (m, 2 H), 1.91 (s, 3 H), 2.40 (m, 1 H), 3.2 - 3.6 (m, 6 H), 3.95 (d, 5.1 Hz, 2 H), 4.3 (m, 2 H), 4.44 (t, 5.2 Hz. 1 H), 6.75 (s, 2 H), 8.35 (s, I H).

^{13}C NMR (DMSO-d_6 δ): 15.1 (2 C, CH_3), 20.5 (CH), 32.6 (CH_2), 35.0 (CH_3), 48.28 (CH_2), 60.6 (CH_2), 61.0 (CH_2), 64.2 (CH_2), 100.2 (CH). 114.9 (C), 142.2 (C), 149.9 (CH), 159.9 (C), 164.3 (C), 170.1 (C).

2-amino-6-chloro-9-cyclopentylpurine

^{1}NMR (DMSO-d_6 δ): 1.65 - 1.80 (m, 2 H), 1.82 - 2.09 (m, 4 H), 2.16 (m. 2 H), 4.76 (m, 1 H), 6.96 (s, 2 H), 8.27 (s, 1 H);

2-amino-6-chloro-7-cyclopentylpurine

'H NMR (DMSO-d_6 δ): 1.70 - 1.95 (m, 4 H), 1.95 - 2.1 (m, 2 H), 2.15 - 2.30 (m, 2 H), 5.11 (m, I H), 6.67 (s, 2 H). 8.53 (s, 1 H)

(R)-2-amino-6-benzyloxy-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine

'H NMR (DMSO-d_6 δ): 1.04 (t, 7.0 Hz, 3 H), 1.06 (t, 7.0 Hz, 3 H), 1.50 (m, 2 H), 1.98 (s, 3 H), 2.43 (m, 1 H), 3.3 - 3.6 (m, 6 H), 3.85 - 4.15 (m,

4 H), 4.48 (t, 5.6 Hz, 1 H), 5.50 (s, 2 H), 6.44 (s, 2 H),7.3 - 7.45 (m, 3 H), 7.5 (m, 2 H), 7.86 (s, I H).

^{13}C NMR (DMSO-d_6 δ): 15.2 (2 C, CH_3), 20.5 (CH), 32.7 (CH_2), 34.0 (CH_3), 44,4 (CH_2), 60.5 (CH_2), 61.0 (CH_2), 64.2 (CH_2), 66.8 (CH_2), 100.4 (CH), 113.6 (C), 128.0 (CH), 128.3 (2 C, CH), 128.4 (2 C, CH), 136.7 (C), 140.2 (CH), 154.7 (C). 159.6 (C), 160.0 (C), 170.3 (C).

(R)-2-amino-6-benzyloxy-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine

'H NMR (DMSO-d_6 δ): 0.97 (t, 7.0 Hz, 3 H), 1.00 (t, 7.0 Hz, 3 H), 1.35 - 1.6 (m, 2 H), 1.88 (s, 3 H), 2.40 (m, 1 H), 3.2 - 3.5 (m, 6 H), 3.86 (m. 2 H), 4.14 (m, 2 H), 4.25 (t, 5.6 Hz,I H), 5.50 (m, 2 H), 6.20 (s, 2 H),7.3 - 7.45 (m, 3 H), 7.5 (m, 2 H), 8.09 (s, I H).

^{13}C NMR (DMSO-d_6 δ): 15.1 (2 C, CH_3), 20.4 (CH). 32.4 (CH_2), 35.0 (CH_3), 48.7 (CH_2), 60.4 (CH_2), 60.9 (CH_2), 64.1 (CH_2), 67.1 (CH_2), 100.3 (CH), 105.7 (C), 128.0 (CH), 128.1 (CH), 128.4 (2 C, CH), 136.3 (C), 145.9 (CH), 156.3 (C), 159.6 (C), 164.2 (C), 170.2 (C).

Table 2

purine	Alkylating agent	solvent	Yield Σ N9 +N7	Ratio N9:N7
2-amino-6-chloropurine	A	DMF	91	4.7
2-amino-6-chloropurine	A	DMSO	91	5.9
2-amino-6-chloropurine	*A, K_2CO_3*	*DMF*	*86*	*4.2*
2-amino-6-chloropurine	*A, tetrabutylN*	*DMF*	*86*	*5.0*
2-amino-6-chloropurine	B	DMF	80	3.8
2-amino-6-chloropurine	B	DMSO	83	4.8
2-amino-6-chloropurine	*A, K_2CO_3 [c]*	*DMF*	*59*	*3.3*
2-amino-6-chloropurine	*A, tetrabutylN[d]*	*DMF*	*75*	*3.7*
2-amino-6-BnO-purine	A	DMF	85	1.6
2-amino-6-BnO-purine	A	DMSO	81	1.7
2-amino-6-BnO-purine	*A, K_2CO_3[c]*	*DMF*	*57*	*1.1*

A: (2S)-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate

B: cyclopentyltosylate

[c]: 1.85 equivalents of K_2CO_3

[d]: tetrabutylammonium salt

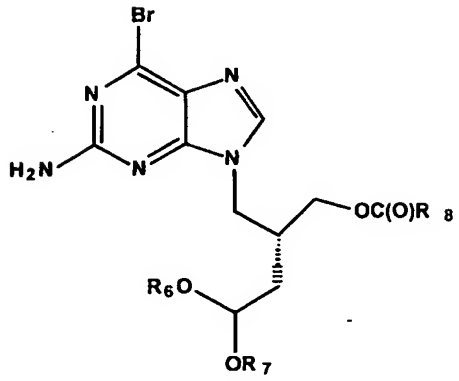
It will thus be apparent that the bulky phosphazine base provided superior regioisomeric control and yield with both alkylating agents used, compared to the conventional alkylation approaches of the purine in conjunction with a base (typically K_2CO_3) or a preformed and dried (due to the water byproduct formed during salt formation) tetrabutylammonium purine salt. It should also be noted that the bulky phosphazine base not only produced the purine salt in situ and without isolation, but also produced the cleanest reaction. The preparation of phosphazenium salt forming bases, otherwise known as Schwesingar bases is described in Schwesinger, R. Chimia 1985 39 269-272 and

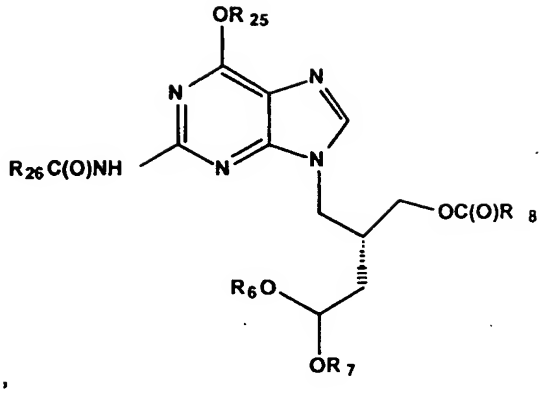
Schwesinger et al Chem. Ber. 1994, 127 2435-2454. As shown above, when applied to the synthesis of purines, they allow alkylation under very mild conditions such as in THF at 35-40°C with the yields of the products approaching quantatitive.

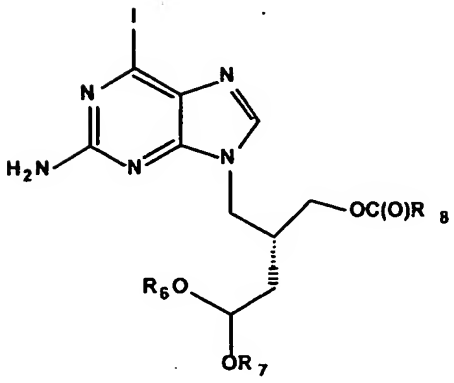
The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosures made herein. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention as defined in the appended claims.

Claims

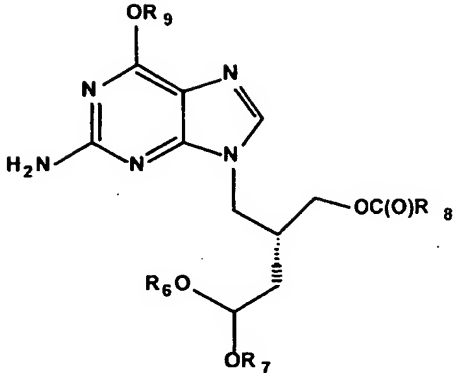
1. A compound of the formula:







or



wherein R_8 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-, R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_9 is an alcohol protecting group, R_{25} is hydrogen or -$C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group and R_{26} is loweralkyl, phenyl or benzyl.

2. The compound of Claim 1, wherein R_6 and R_7 are $-CH_3$ or $-CH_2CH_3$ or R_6 and R_7 taken together are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ and R_8 is CH_3.

3. The compound of Claim 1, wherein R_6 and R_7 are $-CH_2CH_3$ and R_8 is CH_3.

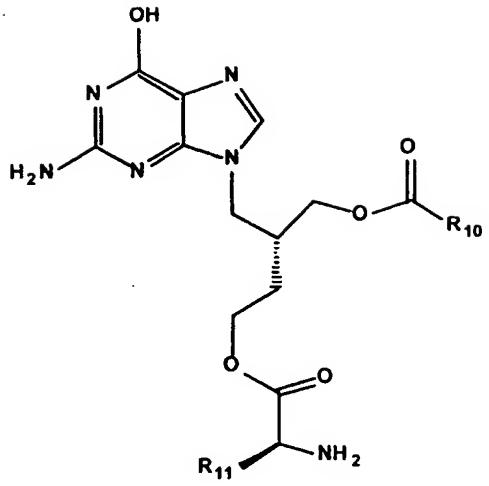
4. The compound of Claim 1, wherein R_6 and R_7 are $-CH_3$ or $-CH_2CH_3$ or R_6 and R_7 taken together are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ and R_8 is $-(CH_2)_{16}CH_3$.

5. The compound of Claim 1, wherein R_6 and R_7 are $-CH_2CH_3$ and R_8 is $-(CH_2)_{16}CH_3$.

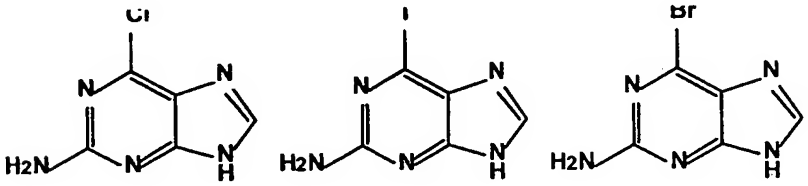
6. The compound of Claim 1, wherein R_8 is $-(CH_2)_{16}CH_3$ or $-CH_3$, R_{25} is hydrogen and R_{26} is $-CH_3$.

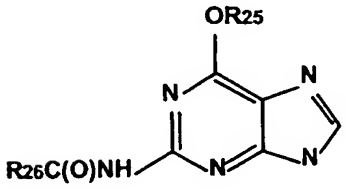
7. The compound of Claim 1, wherein R_8 is $-(CH_2)_{16}CH_3$ or $-CH_3$, R_{25} is $-C(O)N(phenyl)_2$ and R_{26} is $-CH_3$.

8. A process for the preparation of a compound of the formula:



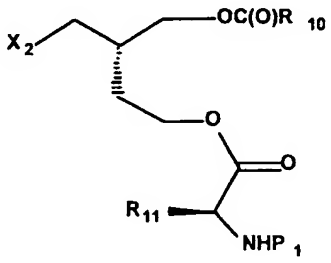
wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising the step of reacting a compound of the formula:





wherein R_{25} is hydrogen or $-C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with

the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group and R_{26} is loweralkyl, phenyl or benzyl;
with a compound of the formula:



wherein X_2 is a halogen or sulfonate leaving group and P_1 is an N-protecting group and R_{10} and R_{11} are as defined above.

9. The process of Claim 8, wherein R_{10} is $-(CH_2)_{16}CH_3$ and X_2 is p-toluenesulfonyloxy.

10. The process of Claim 8, further comprising a base.

11. The process of Claim 10, wherein the base is potassium carbonate, LiH, NaH, KH, NaOH, KOH, lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$ or a sterically bulky amine base.

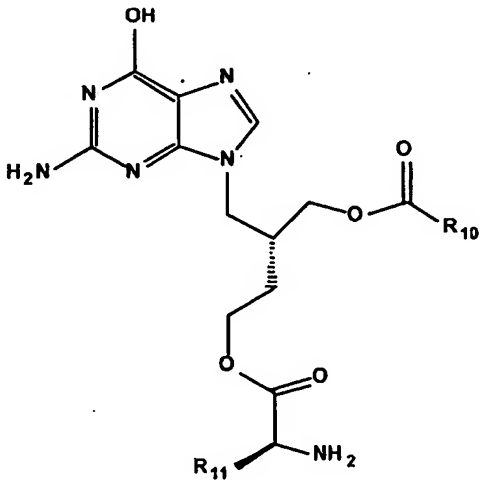
12. The process of Claim 11, wherein the sterically bulky amine base is 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[4.3.0]non-5-ene, tetramethylguanidine, N,N-diisopropylethylamine or a sterically bulky phosphazine base.

13. A process of Claim 12, wherein the bulky phosphazine base is selected from the group consisting of tert-butylimino-

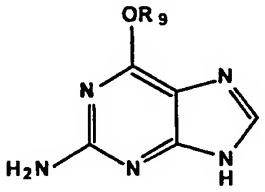
tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)-phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

14. A process according to claim 13, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

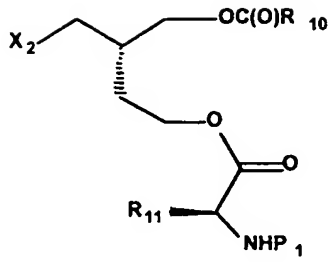
15. A process for the preparation of a compound of the formula:



wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising the step of reacting a compound of the formula:



wherein R_9 is an alcohol protecting group with a compound of the formula:



wherein X_2 is a halogen or sulfonate leaving group and P_1 is an N-protecting group and R_{10} and R_{11} are as defined above in the presence of a base selected from LiH, NaH, KH, NaOH, KOH, lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$ or a sterically bulky amine base.

16. The process of Claim 15, wherein R_{10} is $-(CH_2)_{16}CH_3$ and X_2 is p-toluenesulfonyloxy.

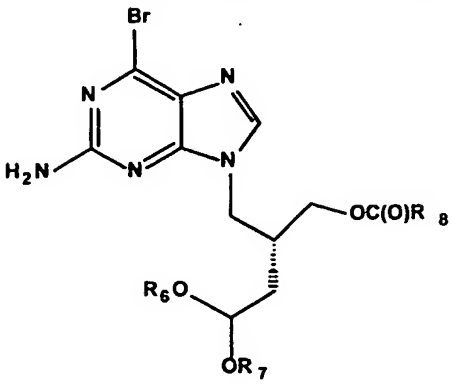
17. The process of Claim 15, wherein R_9 is benzyl.

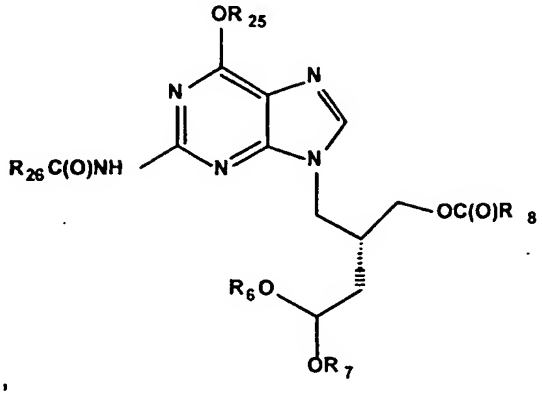
18. The process of Claim 15, wherein the sterically bulky amine base is 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[4.3.0]non-5-ene, tetramethylguanidine, N,N-diisopropylethylamine or a sterically bulky phosphazine base.

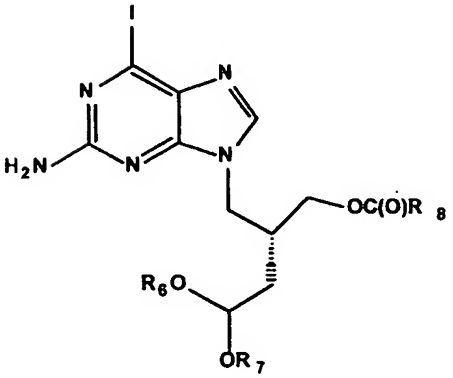
19. The process of claim 18, wherein the sterically bulky amine base is selected from the group consisting of tert-butylimino-tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)-phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

20. The process of claim 19, wherein the sterically bulky amine base is tert-butyliminotri(pyrrolidino)phosphorane.

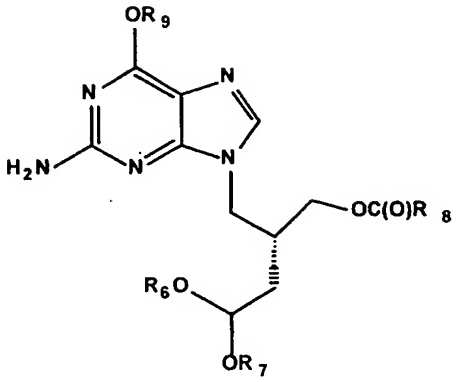
21. A process for the preparation of a compound of the formula:



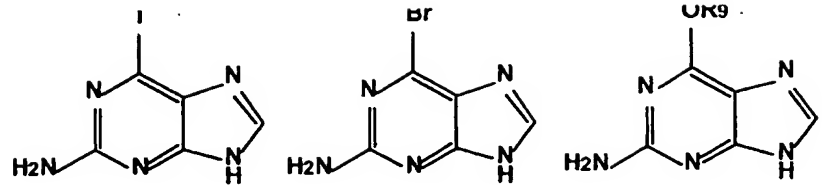


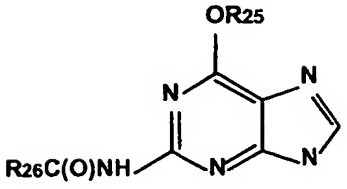


or

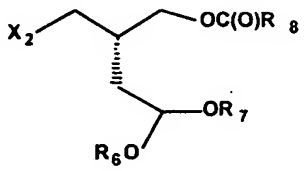


wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-, R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_9 is an alcohol protecting group, R_{25} is hydrogen or -$C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group and R_{26} is loweralkyl, phenyl or benzyl, comprising the step of reacting a compound of the formula:





wherein R_9 R_{25} and R_{26} are as defined above with a compound of the formula:



wherein R_6, R_7, R_8 and R_9 are as defined above and X_2 is a leaving group.

22. The process of Claim 20, wherein R_8 is $-(CH_2)_{16}CH_3$ or $-CH_3$ and X_2 is p-toluenesulfonyloxy.

23. The process of Claim 20, wherein R_9 is benzyl.

24. The process of Claim 20, further comprising a base.

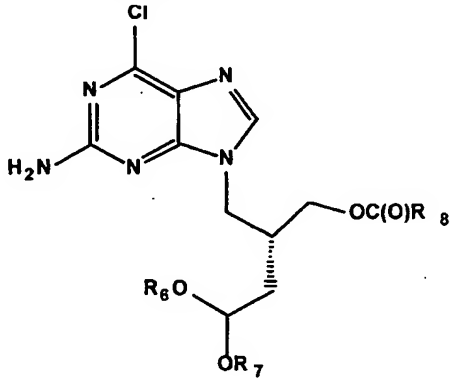
25. The process of Claim 24, wherein the base is potassium carbonate, LiH, NaH, KH, NaOH, KOH, lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$ or a sterically bulky amine base.

26. The process of Claim 25, wherein the sterically bulky amine base is 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[4.3.0]non-5-ene, tetramethylguanidine, N,N-diisopropylethylamine or a sterically bulky phosphazine base.

27. The process of Claim 26, wherein the bulky phosphazine base is selected from the group consisting of tert-butylimino-tri(dimethylamino)-phosphorane, tert-butylimino-tri(pyrrolidino)phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

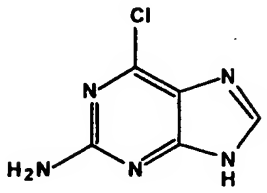
28. The process of Claim 27, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

29. A process for the preparation of a compound of the formula:

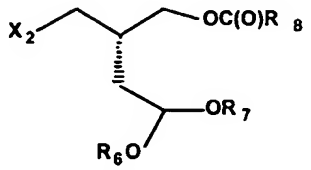


wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$- and R_8 is C_1-C_{21} saturated or

monounsaturated, optionally substituted alkyl comprising the step of reacting a compound of the formula:



with a compound of the formula:



wherein R_6, R_7, R_8 and R_9 are as defined above and X_2 is a leaving group in the presence of a base selected from LiH, $LiN(Si(CH_3)_3)_2$ or a sterically bulky amine base.

30. The process of Claim 29, wherein the sterically bulky amine base is 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[4.3.0]non-5-ene, tetramethylguanidine, N,N-diisopropylethylamine or a sterically bulky phosphazine base.

31. The process of Claim 30, wherein the bulky phosphazine base is selected from tert-butylimino-tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

32. The process of claim 31, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

33. The process of Claim 29, wherein R_8 is $-(CH_2)_{16}CH_3$ or $-CH_3$ and X_2 is p-toluenesulfonyloxy.

34. A process for alkylating a purine base comprising reacting the purine with a sterically bulky phosphazine base prior to, or simultaneously with, addition of the alkylating agent.

35. A process according to Claim 34, wherein the purine is selected from 2-amino-6-halopurine or hydroxy-protected guanine.

36. A process according to Claim 35, wherein the purine-bulky phosphazine base reaction product is not isolated prior to alkylation.

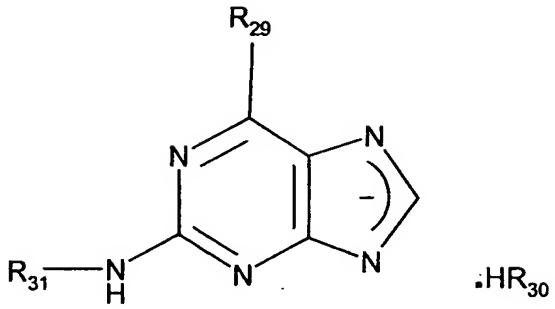
37. A process according to Claim 34, wherein the alklyating agent comprises a tosylate leaving group.

38. A process according to claim 34, wherein the alkylating agent comprises an optionally protected acyclic nucleoside side chain.

39. A process according to Claim 34, wherein the bulky phosphazine base is selected from the group consisting of tert-butylimino-tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)-phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

40. A process according to claim 39, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

41. A phosphazenium salt of the formula:



wherein R_{31} is H or -C(O)NR_{26}, R_{26} is lower alkyl, phenyl or benzyl, R_{29} is Br, Cl, I or OR_9, wherein R_9 is an hydroxy protecting group and R_{30} is derived from a bulky phosphazine moiety.

42. A salt according to Claim 41, wherein the bulky phosphazine moiety is derived from tert-butylimino-tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

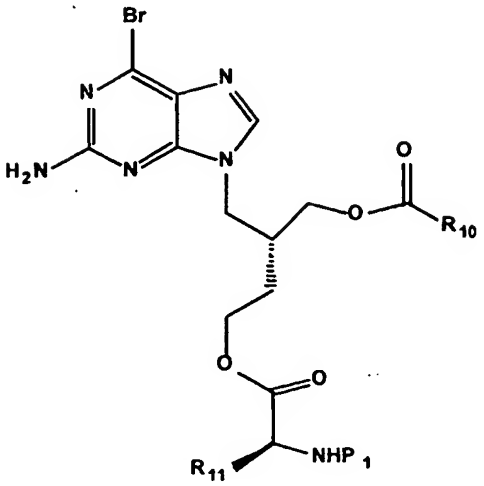
43. A salt according to claim 42, wherein the bulky phosphazine moiety is derived from tert-butyliminotri(pyrrolidino)phosphorane.

44. A salt according to claim 42, wherein R_{27} is chloro.

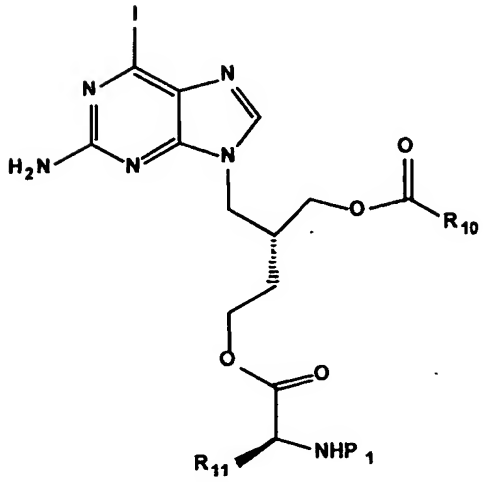
45. A salt according to claim 42, wherein R_{27} is iodo.

46. A salt according to claim 42, wherein R_9 is –C(O)$NR_{27}R_{28}$ where R_{27} and R_{28} are independently selected from lower alkyl, phenyl or benzyl or R_{27} and R_{28} form a pyrrolidinyl group or a piperidinyl group.

47. A compound of the formula:



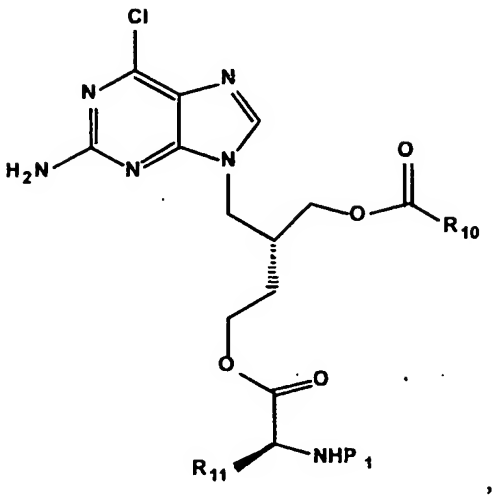
or



wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is an N-protecting group.

48. The compound of Claim 47, wherein R_{10} is $CH_3(CH_2)_{16}$-, R_{11} is isopropyl and P_1 is benzyloxycarbonyl, t-butyloxycarbonyl, allyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

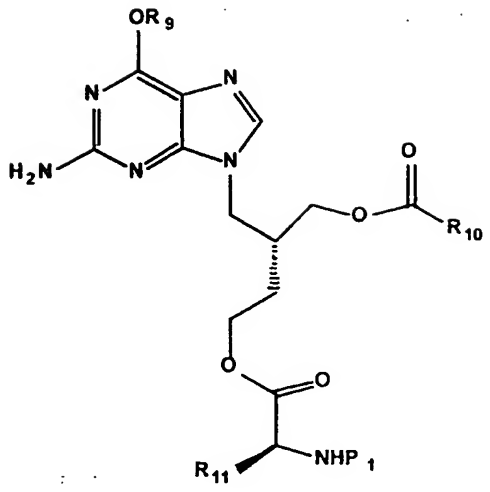
49. A compound of the formula:



wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is benzyloxycarbonyl, allyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

50. The compound of Claim 49, wherein R_{10} is $CH_3(CH_2)_{16}$- and R_{11} is isopropyl.

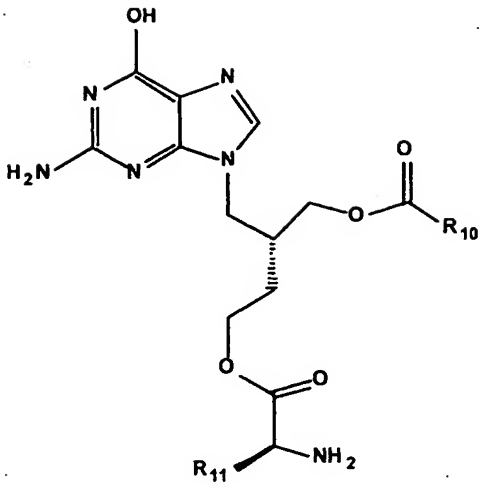
51. A compound of the formula:



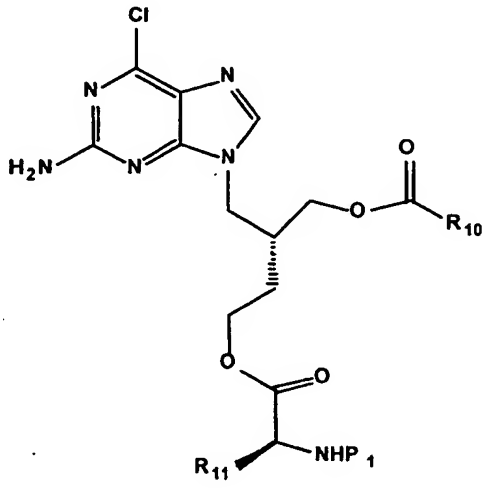
wherein R_9 is an alcohol protecting group, R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is t-butyloxycarbonyl, allyloxycarbonyl or trichloroethoxycarbonyl.

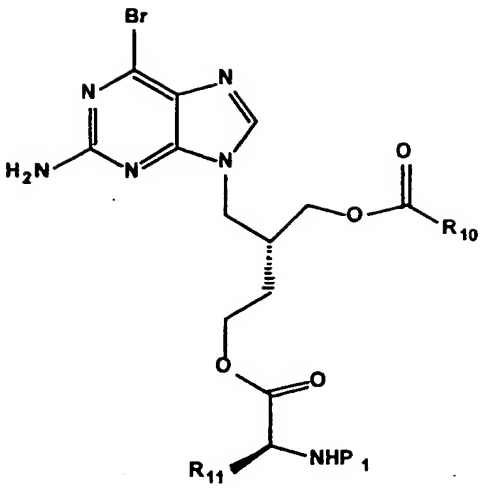
52. The compound of Claim 51, wherein R_9 is benzyl, R_{10} is $CH_3(CH_2)_{16}$- and R_{11} is isopropyl.

53. A process for the preparation of a compound of the formula:

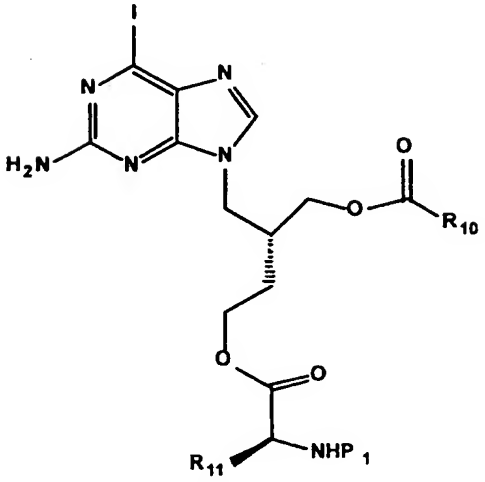


wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising hydrolysis of a compound of the formula:



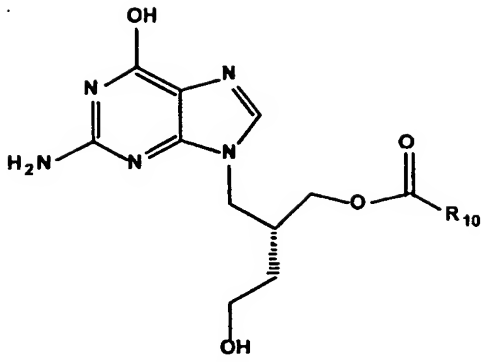


or



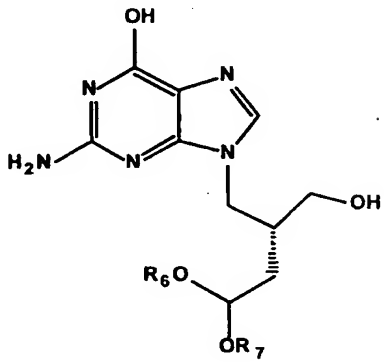
wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is an N-protecting group.

54. A process for preparing a compound of the formula:

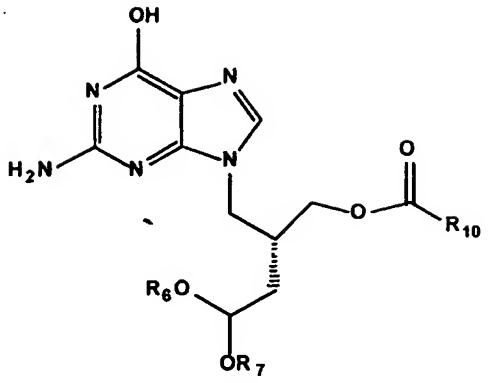


wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl comprising:

a) reacting a compound of the formula:



wherein wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ with $R_{10}COOH$ or an activated derivative thereof wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl to provide a compound of the formula:



wherein R_6, R_7 and R_{10} are defined as above,

b) deprotecting the acetal of the product of step a) and

c) reducing the aldehyde substituent of the product of step b),

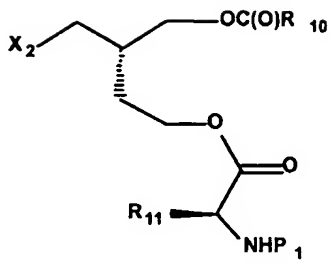
characterized in that the products of steps a) and b) are not isolated.

55. The process of Claim 54, wherein R_6 and R_7 are $-CH_2CH_3$ and R_{10} is $-(CH_2)_{16}CH_3$.

56. The process of Claim 54, wherein the activated derivative of $R_{10}COOH$ is $CH_3(CH_2)_{16}C(O)OC(O)C(CH_3)_3$.

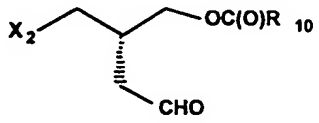
57. The process of Claim 54, wherein the acetal is deprotected with triflic acid and the aldehyde substituent of the product of step b) is reduced with borane t-butyl amine complex.

58. A process for preparing a compound of the formula:



wherein X_2 is a halogen or sulfonate leaving group, P_1 is an N-protecting group, R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl comprising

a) reducing to an alcohol the aldehyde substituent of a compound of the formula:



wherein X_2 and R_{10} are as defined above and

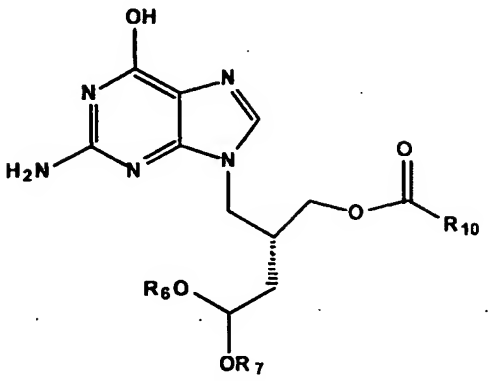
b) reacting the product of step a) with $P_1NHCH(R_{11})COOH$ or an activated derivative thereof or with $P_1NHCH(R_{11})C(O)$-O-$C(O)CH(R_{11})NHP_1$ wherein R_{11} and P_1 are as defined above,

characterized in that the product of step a) is not isolated.

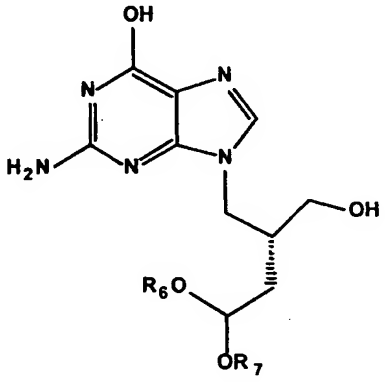
59. The process of Claim 58, wherein X_2 is p-toluenesulfonyloxy and R_{10} is $-(CH_2)_{16}CH_3$.

60. The process of Claim 58, wherein X_2 is p-toluene-sulfonyloxy, R_{10} is $-(CH_2)_{16}CH_3$, R_{11} is isopropyl and P_1 is benzyloxycarbonyl, t-butyloxycarbonyl or allyloxycarbonyl.

61. A process for the preparation of a compound of the formula:



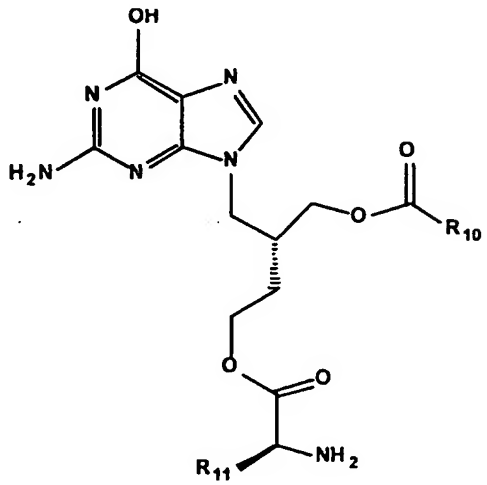
wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ and R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, comprising reacting a compound of the formula:



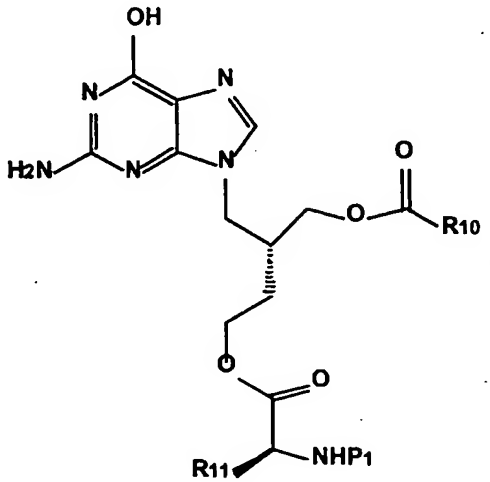
wherein R_6 and R_7 are as defined above with an activated derivative of $R_{10}COOH$, said activated derivative being prepared in situ.

62. The process of Claim 61, wherein the activated derivative of $R_{10}COOH$ is $CH_3(CH_2)_{16}C(O)OC(O)C(CH_3)_3$.

63. A process for the preparation of a compound of the formula:

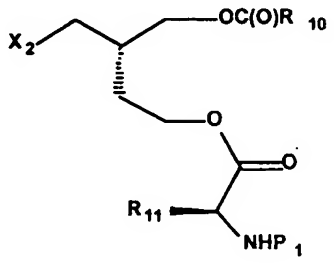


wherein R_{10} is C_3-C_{21} saturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising hydrogenation of a compound of the formula:



wherein R_{10} and R_{11} are as defined above and P_1 is benzyloxycarbonyl with a hydrogenation catalyst selected from $Pd/BaSO_4$ and $Pd/BaCO_3$.

64. A compound of the formula:



wherein X_2 is p-toluenesulfonyloxy, R_{10} is $-(CH_2)_{16}CH_3$, R_{11} is isopropyl and P_1 is t-butyloxycarbonyl or allyloxycarbonyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01339

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 473/18, C07D 473/32, C07D 473/00 // C07C 309/45
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9730051 A1 (MEDIVIR AB), 21 August 1997 (21.08.97)	1-33,47.57, 61-63
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X	WO 9730052 A1 (MEDIVIR AB), 21 August 1997 (21.08.97)	1-33,47-57, 61-63
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P,A	WO 9834917 A2 (ABBOTT LABORATORIES), 13 August 1998 (13.08.98)	1-63
P,X	see page 16, 17 and claims 64-66	64
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999	24 November 1999 (24.11.99)
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01339

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9408951 A1 (MONSANTO COMPANY), 28 April 1994 (28.04.94)	13,14,19,20, 27,28,31,32, 39,40,42-43

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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/11/99

International application No.
PCT/SE 99/01339

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